Battle Casualties in Korea

Studies of the Surgical Research Team

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Battle Casualties in Korea:
Studies of the Surgical Research Team

Volume II: Tools for Resuscitation

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Chapter 1

Introduction

Lieutenant Colonel William H. Crosby, MC, USA

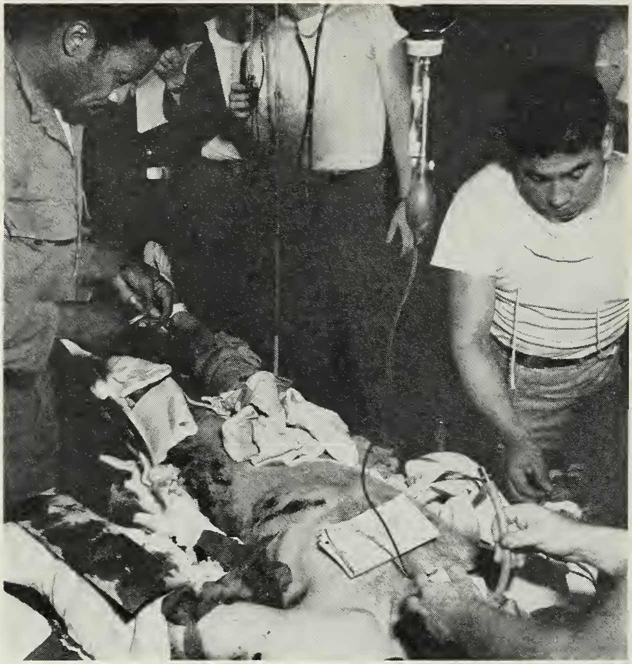
Volume I of this series has described the response of the body's several systems to injuries produced by wounds received in combat. Great emphasis was placed upon the nature of this response, that it is not confined to the wounded tissues or systems or organs alone but involves the entire physiologic economy for a prolonged period of time. The damage done by wounding is not confined to the instant of impact but continues so long as bleeding, infection, pain, fear and exposure continue. When the wound is a light one, the response to injury is small and may be self-limited. But unless help is given to those with grave wounds the injury and response proceed crescendo, and some of the reactions may themselves become injurious. "Resuscitation" is the name given to this necessary help, and the means whereby the help is administered are lumped together as the "tools for resuscitation."

Of these tools, surgery is the most important, but the others are essential. They preserve the life of the wounded man, prepare him for the surgical procedure, help him to withstand it and sustain him until he has recovered and convalescence has begun. When the tools for resuscitation are used successfully, they reinforce the body's response to injury so that the damage is brought quickly under control and healing can occur.

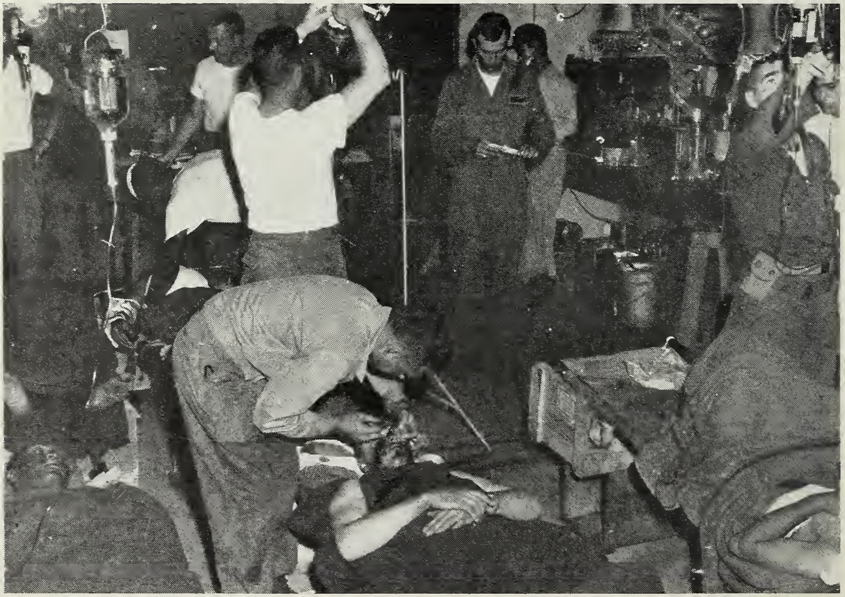
This second volume of the series is concerned with the nature and use of these agents. We know that none of them is perfect. Almost without exception they cause some further injury in addition to their help. Their skillful use takes this into account and seeks to minimize the damage they may do while taking full advantage of the help.

Tools for Resuscitation

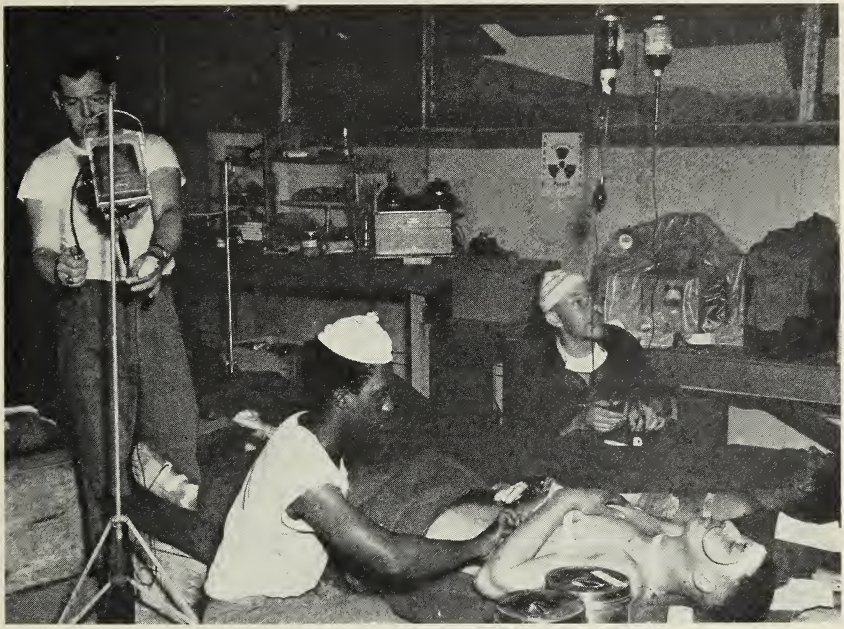
Those charged with research of the wounded and their care must recognize the double edge these tools possess and evaluate each one. They must seek to learn how and to what extent these agents help the wounded; they must also gauge the damage that is done in using them, find how the damage may be minimized and how the tools may be improved. Investigation of this sort is difficult. Most of it must confine itself to careful observation of what happens while the wounded



The many aspects of resuscitation.



A false appearance of confusion masks a highly efficient resuscitative team.



Temporary diversion of the research space and personnel to resuscitation at a time when the clinical facilities were completely overloaded with casualties.

The breakthrough in the closing months of the conflict filled the entire hospital with casualties. Clinical observations replaced physiologic measurements as the modus operandi of the research unit.

man is treated as best we know how. If experiments are devised, they must never compromise the program of resuscitation. Necessity for speed prevents some observations. The welfare of the wounded prevents adequate controls in many phases of research as does the infinite variety of the injuries and the individuals who sustain them. The number of tests that may be done is limited, so that "points of interest" must be subordinated to "points of importance." The limitations of such research are easily recognized. However they may blur the significance of the results, they cannot be avoided. In spite of them, much useful knowledge can be gained and was gained in Korea. It was found, for instance, that the "massive" transfusions given to the most severely wounded were not too large, that the "old" blood used for them had not deteriorated unduly, that plasma substitutes could be used to "stretch" the supply of blood, that the best anesthetic was the least that could do the job. The search to improve the tools of resuscitation was not confined to the bedside. There was a constant effort to provide better agents, fresher blood, even better and safer packaging. The list does not end here, as one may learn from study of the present volume and its companions.

Chapter 2

Studies of the Absorption and Equilibration of Water (Deuterium Oxide) from the Gastrointestinal Tract Following Injury*

A Study of Battle Casualties in Korea

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This study of the absorption of deuterium oxide from the gastrointestinal tract and its equilibration has as its primary purpose the investigation of the limitations of oral fluid administration to mass casualties. The administration of fluids to mass casualties poses problems which have not been previously explored.

The secondary purpose of this study was to gain factual observations upon which to base routine postoperative care in the field of fluid administration.

Finally, the authors hoped to gain additional information on the nature and scope of the systemic response to injury. Studies by the Surgical Research Team in Korea demonstrated that every organ and system which could be studied responds to severe trauma. In general, this response is not of a few moments' or hours' duration but is a response which lasts for days or weeks. This study was, therefore, designed to extend these observations to the response of the gastrointestinal tract to injury.

Schloerb and his co-workers[9] described an equilibration curve in venous blood following the oral ingestion of deuterium oxide in a human subject. They found an equilibration time of approximately 3 hours. This study was designed to extend this observation in the normal and to study the equilibration time after injury.

Material and Methods

The study was carried out at a Forward Surgical Hospital on the Eastern Front in Korea during 1952 to 1953. During this time the

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average time between wounding and reaching the forward hospital was 3.5 hours. Healthy young soldiers in noncombat areas volunteered as controls. The wounded subjects were young battle casualties in the 18 to 34 age range. Those casualties who were studied immediately after arrival at the hospital were selected on the basis that they had fasted for 5 to 12 hours prior to injury and gastric suction had confirmed the presence of an empty stomach. Each casualty was given 50 to 100 grams of deuterium oxide (heavy water) as isotonic saline. The deuterium oxide was 99.8 per cent pure.

Gastrointestinal Deuterium Oxide Absorption

Venous samples were obtained prior to ingestion of D_2O and at frequent periods thereafter. Several were studied at 5, 10, 15, 20, 30, 45, 60, 90, 180 and 240 minutes after ingestion. In addition, when feasible, subsequent samples were obtained after a prolonged period of time. Other casualties were, of necessity, studied less intensively but enough points on the equilibration curve were obtained to describe its pattern. The venous blood was centrifuged, the plasma withdrawn, placed in a paraffin-sealed test tube, and shipped via air to Washington, D. C., for analysis. Deuterium analyses were performed at the National Bureau of Standards. The deuterium content of the samples was determined by converting the "free water" to hydrogen over hot magnesium. Mass-spectrometric analyses of the isotopic hydrogens were made with a Consolidated 21–103 mass spectrometer using established technics including operational procedures suggested by Honig.[4] The hydrogen samples were cooled to 190° C to prevent possible introduction of water vapor. At least three determinations were made of each duplicate sample. Analyses of samples containing less than 0.5 atom per cent D were generally repeated if the duplicates disagreed by more than 0.01 atom per cent. The reproducibility of a single determination was usually of the order of 0.003 atom per cent D.

Experiments with nearly pure D_2O indicate the technics used in the conversion process result in memory effects of considerably less than 1 per cent. Analyses of test mixtures of hydrogens indicated the mass spectrometer uncertainty to be of the order of 1 per cent for samples containing about 0.3 atom per cent D. However, the necessary delay in receiving, converting and analyzing the samples undoubtedly contributes to the experimental error. Furthermore, although all samples were intended to be hermetically sealed, a number showed definite evidence of evaporation in transit. Those showing marked evaporation were not analyzed.

Gastrointestinal Absorption in the Uninjured Soldier

Six healthy soldiers volunteered as controls. All six had been fasting for 14 hours and continued to fast throughout the period of study. Each was given 100 grams of deuterium oxide orally.

The results are depicted in Figures 1 to 6. Equilibration of the concentration of deuterium in the venous plasma was complete in 120 minutes. In several instances equilibration appeared to be complete within 90 minutes. Furthermore, without exception, the venous concentration at 30 minutes demonstrated evidence of absorption of an appreciable amount of deuterium.

Absorption of water obviously occurred in the normal and in many of the wounded men. This was demonstrated by control of thirst, maintenance of urinary output, and the solid consistency of the stools. That the curve of absorption is directly related to the curve of equilibration of deuterium oxide has not been absolutely proved. Evidence is presented which suggests that the two are directly related but the term absorption is used with this reservation throughout the paper.

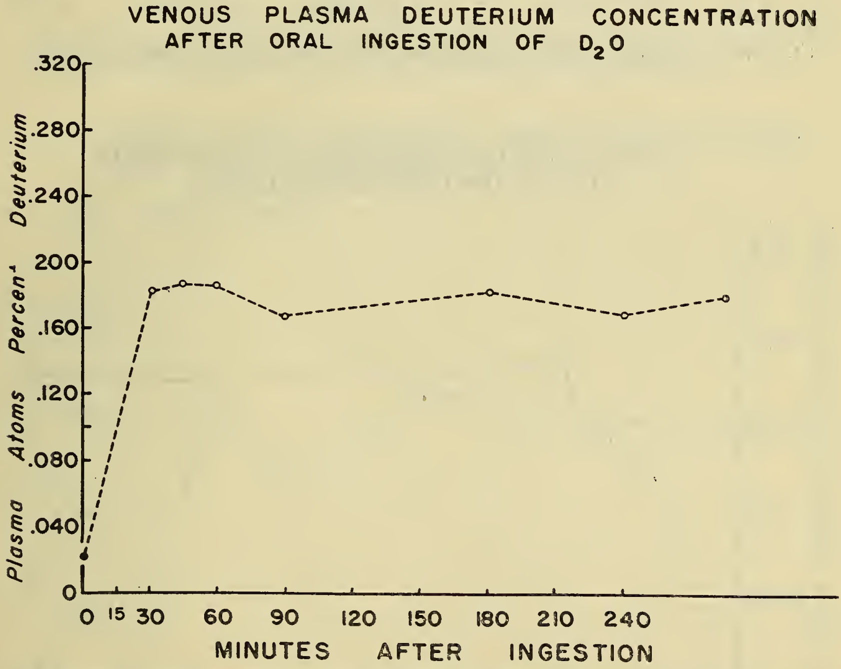

FIGURE 1. Demonstrating the very rapid equilibration in the control subject.

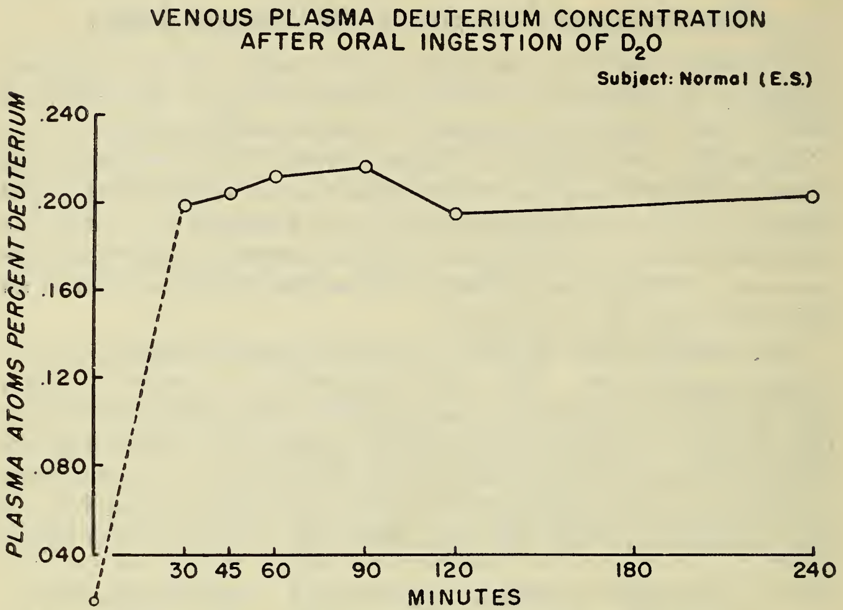

FIGURE 2. Demonstrating a similar equilibration curve in a second subject.

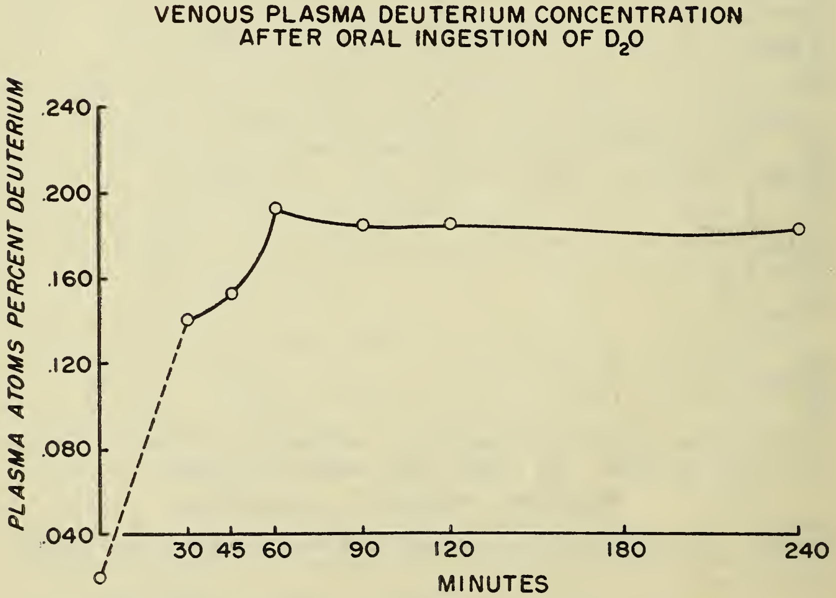

FIGURE 3. Demonstrating equilibration within 90 minutes.

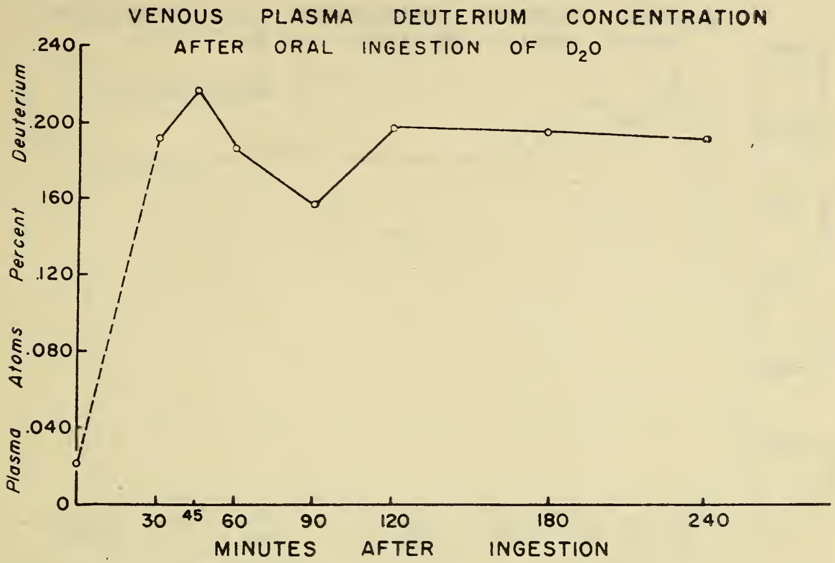

FIGURE 4. Equilibration appears to have been reached within 120 minutes. The initial rise and fall in venous deuterium concentration has been noted repeatedly and appears to be a valid observation in such instances.

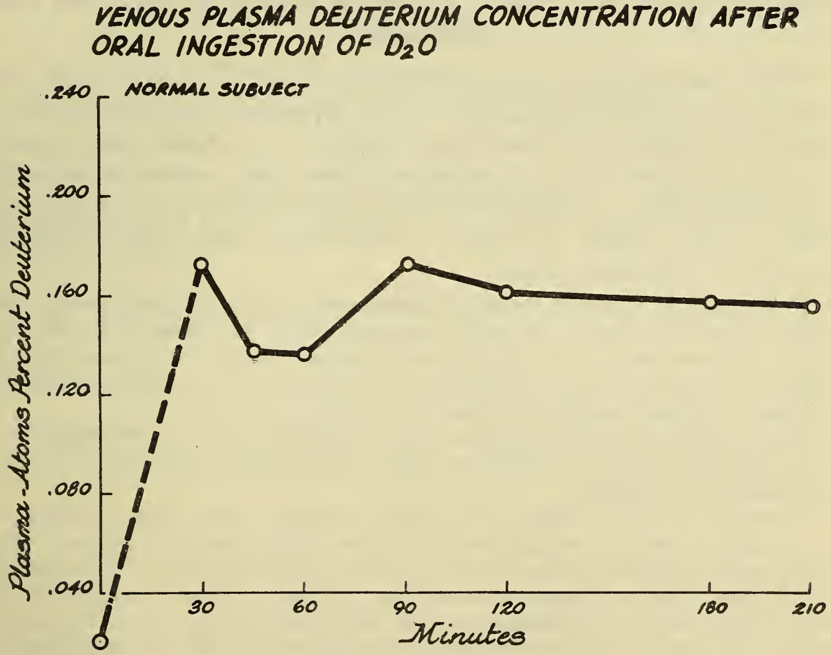

FIGURE 5. Equilibration time 120 minutes.

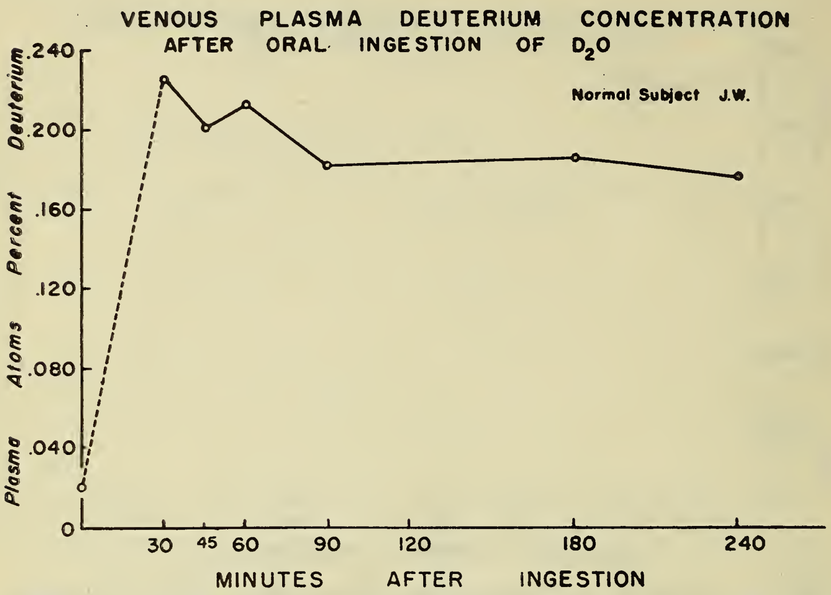

FIGURE 6. Equilibration time approximately 90 minutes. Note, however, the venous concentration is high within 30 minutes after ingestion.

Gastrointestinal Absorption Following Injuries of the Chest and Extremities

Three casualties were selected for study because their wounds did not include abdominal injuries. These three men had wounds which were representative of three types of injuries seen, namely, perforation of the chest, traumatic amputation of the foot, and a moderately severe flash burn. Emphasis was placed upon studying these men shortly after injury in order to determine their gastrointestinal function in this early period.

Patient No. 1. This 21-year-old Korean soldier suffered severe second and third degree flash burns of the scalp, face, neck, hands and wrists on 22 January 1952. He was admitted to the Forward Surgical Hospital 1 hour after injury. His vital signs were normal except for a tachycardia. His hematocrit was 50 per cent. He had received no therapy at this time.

Three hours after injury and 8 hours after ingestion of food or water, he was given orally 100 grams of deuterium oxide. The venous equilibration curve is demonstrated in Figure 7.

Patient No. 2. This 20-year-old South American soldier was wounded on 17 January 1952 by machine-gun fire. The bullet penetrated his left lung, producing a large hematoma of the lung but no pneumothorax. He arrived at the Forward Surgical Hospital 3 hours after injury and appeared to be in a state of incipient shock. Débridement of the superficial tissues was performed 6 hours after injury under ether-nitrous oxide anesthesia. His subsequent course was uneventful.

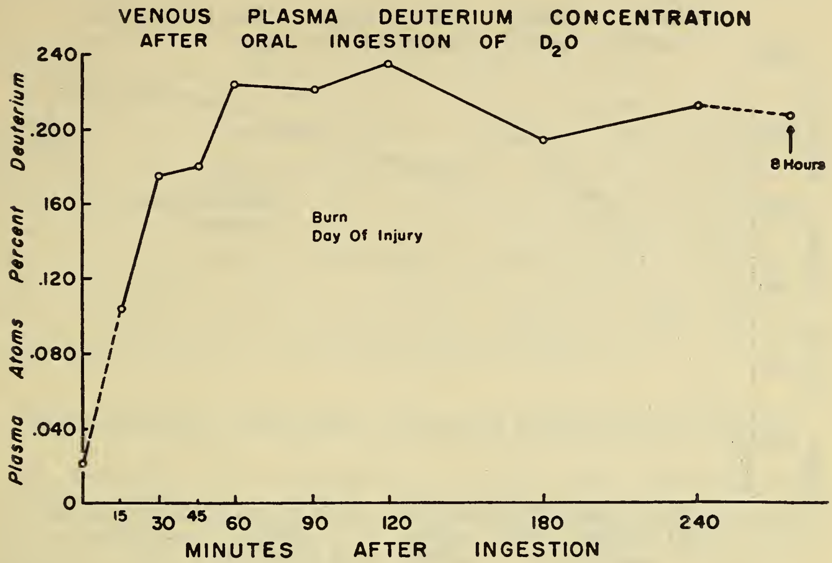

FIGURE 7 (Patient No. 1). This soldier suffered a severe flash burn (second and third degree) of scalp, face, neck, hands and arms. This study, performed prior to therapy, reveals fairly rapid absorption of water from the gastrointestinal tract as indicated by equilibration time.

After having fasted for 24 hours after injury, he was given 100 grams of deuterium oxide orally. The only medication except antibiotics which he had received subsequent to débridement was codeine, 65 mg., 7 hours prior to the study. The equilibration curve of the deuterium is shown in Figure 8.

At the conclusion of the deuterium study, the casualty was given 100 grams of glucose orally. This glucose tolerance study (Table 1) demonstrated the rapid absorption of glucose.[5] The rising limb of the glucose tolerance curve is very similar to the corresponding phase of the deuterium curve. This suggests that the deuterium was absorbed from the bowel by an active process rather than simply by diffusion.[2,3]

Table 1. Blood Glucose Concentration Following Oral Administration of 100 Grams of Glucose

(Patient No. 2)

Minutes After Ingestion	Blood Glucose* mg./100 ml.	Minutes After Ingestion	Blood Glucose* mg./100 ml.
0	95	90	165
30	177	120	123
45	217	180	105
60	237	240	71

*Analysis by the Folin-Wu Method.

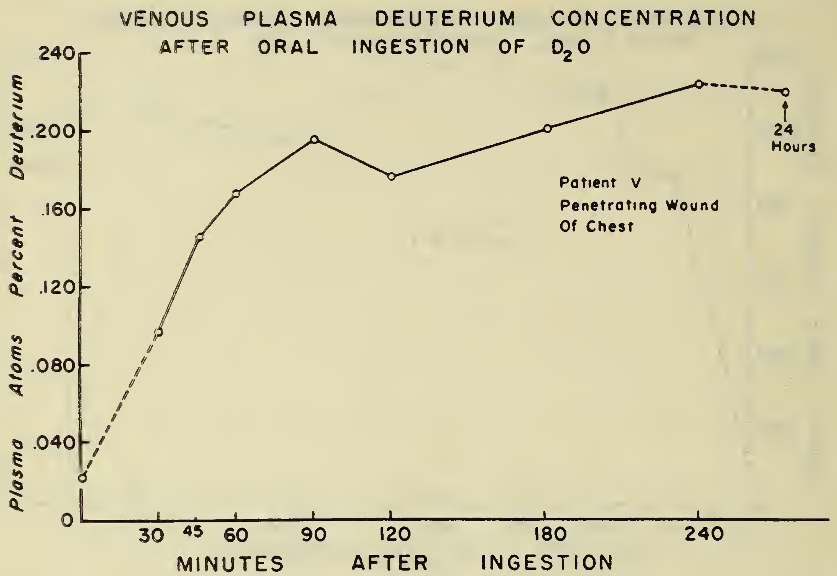

Figure 8 (Patient No. 2). This soldier had received a perforating wound of the lung on the previous day. Operation was limited to local débridement of the soft tissues. Note that the equilibration of deuterium, although somewhat slower than normal, proceeds rapidly during the period of study.

Patient No. 3. This 34-year-old Korean Service Corpsman was injured on 17 May 1952 when he stepped on a land mine. The injury included a traumatic amputation of the right foot above the ankle. In addition, there were penetrating wounds of the left leg and right hand. Hemorrhage from the amputation stump was controlled by a tourniquet.

Two hours after injury he was admitted via helicopter to the Forward Surgical Hospital. His blood pressure was 160/90, pulse 112, hematocrit 40 per cent. He appeared to be severely injured and in a state of incipient shock. Within the first hour after admission, he received 500 ml. of blood. At this time, 3 hours after injury and prior to operation, a Levin tube was inserted into the stomach and the stomach emptied of a small amount of clear gastric juice. Deuterium oxide, 100 grams, was then instilled through the tube.

Re-amputation and débridement were subsequently performed under pentothal-nitrous oxide anesthesia.

By the third postoperative day, his course was smooth. Peristalsis was active and he had one bowel movement since operation. At this time, after fasting for 12 hours, the patient was again given deuterium oxide, 100 grams, orally. The results of the two studies are demonstrated in Figure 9.

These three soldiers were all severely injured men. They fell into a similar functional pattern. All three were treated with oral fluids only. Thirst was controlled and urinary output was maintained by oral therapy. Equilibration was slower than normal in all three casualties but was fairly rapid in the first two. The third soldier had an equilibration rate which was definitely slower than normal, but which increased during the 3 days following injury.

A fourth casualty with gasoline burns of the face, neck, scalp, hands and wrists was given glucose (100 grams) orally, immediately after injury and again the following day. On the day of injury, the blood glucose rose from 163 mg. per 100 ml. (fasting) to 314 mg. after 90 minutes. On the following day, the blood glucose rose from 120 mg. per 100 ml. (fasting) to 240 mg. after 90 minutes. This observation was repeatedly noted in a study of the metabolic response of the battle casualties and demonstrated the residual absorptive function of the gastrointestinal tract after peripheral injuries.[5]

Gastrointestinal Absorption Following Intraperitoneal Injuries

Six casualties with intraperitoneal injuries and one with retroperitoneal injuries were studied. Two patients were studied immediately after injury and prior to surgery. The others were studied during the postoperative period.

Patient No. 4. This young Turkish soldier was wounded at noon on 29 February 1952 by artillery shell fragments. The fragments penetrated the right side of the chest, the right lung and the right side of the liver. He arrived at the forward hospital 3.5 hours later by helicopter. His blood pressure at this time was 46/20 and he was in a state of severe shock. After 1,500 ml. of blood his pressure had risen to 70/40 and his blood volume measurement (T–1825 dye method) demonstrated a residual deficit of 19 per cent. At this time, prior to operation and prior to any medication, he was given 100 grams of deuterium oxide orally (Fig. 10). He remained hypotensive throughout the ensuing 30 minutes of the study.

Subsequently, he underwent a right exploratory thoracotomy under nitrous oxide and ether. The diaphragm was opened and the liver was drained subdiaphragmatically. The pleural cavity was drained to an underwater seal.

His subsequent course was smooth. The deuterium study was repeated on the fifth day after injury.

Patient No. 5. This 24-year-old American soldier was wounded at 1635 hours 10 May 1952 by mortar shell fragments. The wound included a massive wound of the ascending colon necessitating a right colostomy. On admission to the forward hospital, 3 hours after injury, he was in excellent condition. His blood pressure was 120/60, pulse 92 per minute. His plasma volume measurement (T–1824 dye method) demonstrated a deficit of 14 per cent.* His hematocrit was 54 per cent.

At this time, prior to operation, he was given 100 grams of deuterium oxide by mouth (Fig. 11).

After the conclusion of the study, his stomach was emptied and found to contain 32 ml. of fluid containing only 0.3 per cent of the ingested deuterium.

Patient No. 6. This 22-year-old American soldier had a perforation of the bowel 6 or 8 hours prior to laparotomy. Operation was performed under nitrous oxide-ether anesthesia. He was found to have an advanced peritonitis.

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*Normal plasma volume calculated on basis of 45 ml. per kilogram of body weight.

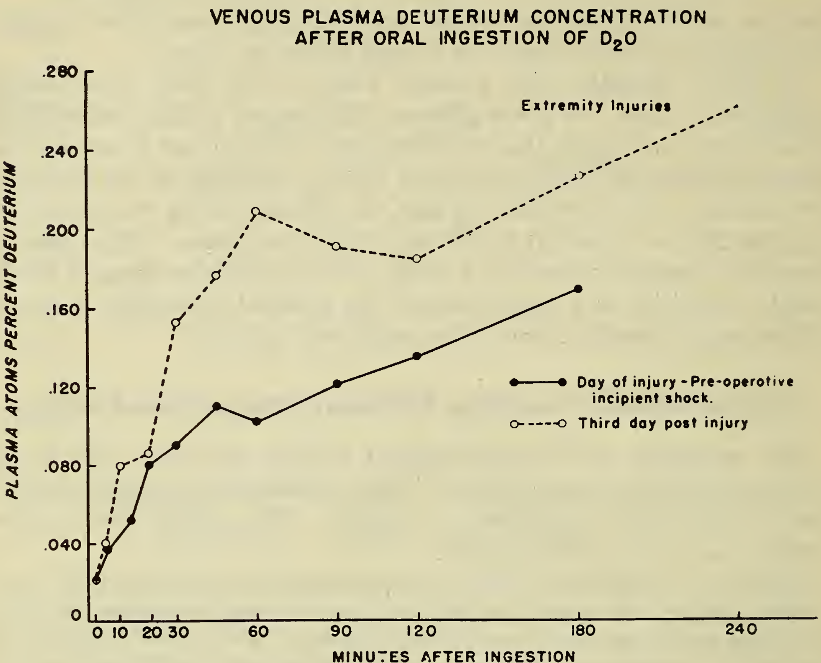
VENOUS PLASMA DEUTERIUM CONCENTRATION AFTER ORAL INGESTION OF D_2O

FIGURE 9 (Patient No. 3). This corpsman had severe wounds of the extremities and was in a state of incipient shock when studied prior to therapy. Equilibration proceeded fairly rapidly although slower than it did 3 days later. On the third day post-injury, equilibration, although faster, was still slower than normal. A state of equilibrium was not reached within 4 hours. Throughout the postoperative period oral intake of water permitted adequate hydration as indicated by lack of thirst and by urinary output.

Note. The concentration of deuterium for the second study has been corrected for the residual plasma deuterium concentration from the previous study.

On the first postoperative day, his condition was good. At this time, his blood volume deficiency was measured at 2 per cent. His hematocrit was 49 per cent. He was then given deuterium oxide, 100 grams, orally. The study was terminated after 120 minutes when the patient vomited.

The study was repeated on the fourth postoperative day (Fig. 12). By this time, peristaltic activity seemed normal by auscultation.

Patient No. 7. This 21-year-old American soldier was shot through the stomach, jejunum and colon by a .45 caliber pistol at 1500 hours on 24 January 1952. He arrived at the forward hospital 2 hours later. He was given 500 ml. of blood prior to operative repair which was done under pentothal, nitrous oxide and ether. At the beginning of operation, his systolic blood pressure dropped to 90 mm. Hg., so he was given a second 500 ml. of blood.

On the day following injury, his stomach being empty, he was given 100 grams of deuterium oxide through the Levin tube (Fig. 13). At the conclusion of the study, one-third of the deuterium was recovered from the stomach. On the following day the patient developed evidence of a spinal cord paralysis which was apparently due to indirect trauma from the missile. He became severely hypotensive and died a few hours later.

Autopsy revealed a generalized peritonitis.

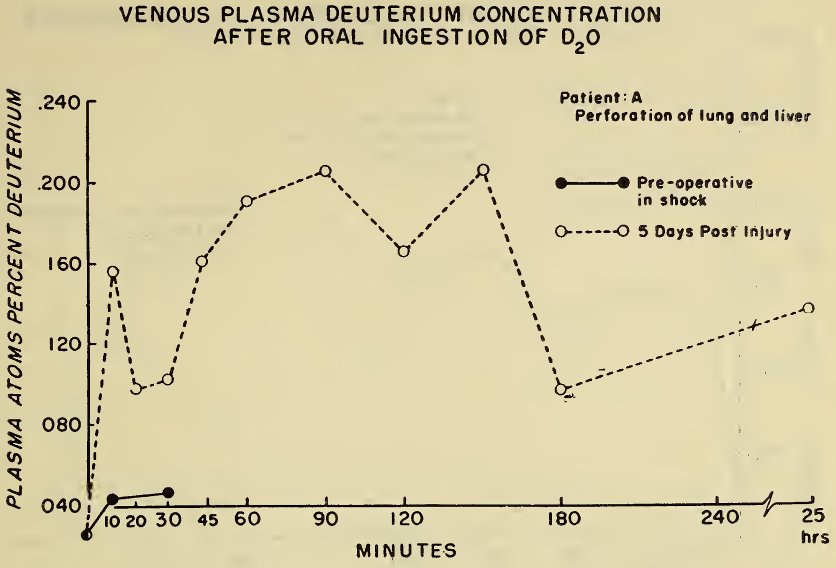

FIGURE 10 (Patient No. 4). This wound did not directly involve the bowel. It consisted of a penetration of the lung and liver with a mild hemoperitoneum. On admission, with the patient in shock, absorption of deuterium was negligible. By the fifth day his bowel activity was clinically normal but his circulatory system remained quite unstable. Absorption had improved but equilibration was not complete after 3 hours. The prolonged period of elevation in plasma concentration may be the result of circulatory inefficiency.

Patient No. 8. This 25-year-old American soldier was admitted to a forward hospital a few hours following a perforation of the bowel. Laparotomy was performed about 12 hours after injury under spinal anesthesia and the perforation was closed. A widespread peritonitis had developed.

On the first postoperative day his temperature was 99.8°, orally, pulse 100, respiration 20 per minute. No peristalsis could be heard. His stomach having been emptied via a Levin tube, he was given 100 grams of deuterium oxide through the tube.

His plasma deuterium curve is demonstrated in Figure 14.

Patient No. 9. This 21-year-old American soldier was wounded at 0230 hours 21 February 1952 when shot through the abdomen with a carbine. The missile perforated the jejunum and the colon. On admission to the Forward Surgical Hospital by ambulance at 0800 hours, his blood pressure was 70/60, pulse 124 per minute. The performation of the small bowel was closed and a colostomy was performed.

Peristalsis became audible on the fourth day after injury and by the sixth day after injury his bowels were moving normally. His oral temperature still rose to 102° daily for several days thereafter.

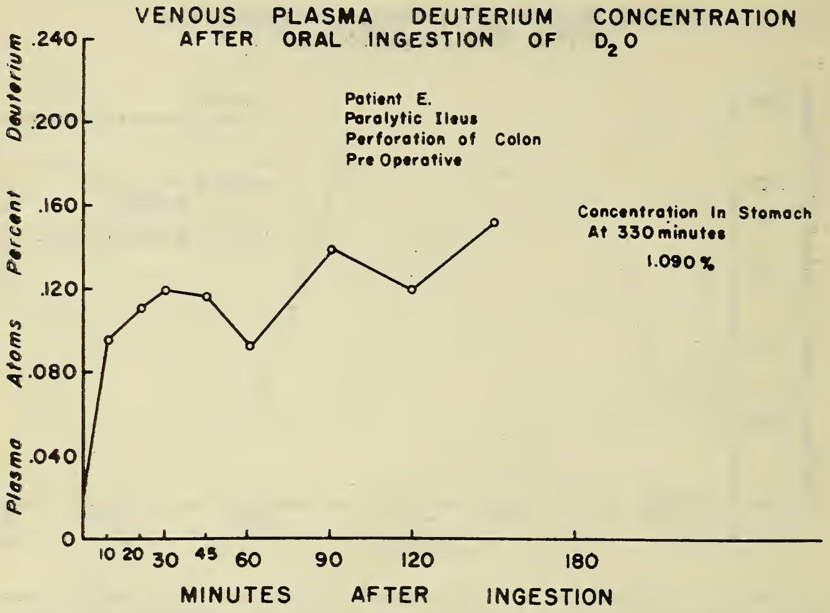

FIGURE 11 (Patient No. 5). The plasma deuterium concentration rose rapidly but equilibration was slow. After 330 minutes, only 32 ml. of fluid containing 0.3 per cent of the ingested deuterium could be found in his stomach.

By the tenth day after injury he was afebrile and his bowels had been moving normally each day for the preceding 7 days. At this time he was given 100 grams of deuterium oxide by mouth. The resultant curve of plasma deuterium concentration is demonstrated in Figure 15.

Patient No. 10. This 41-year-old Korean Service Corpsman was wounded in the back by mortar shell fragments at 1300 hours on 15 January 1952. On admission to the forward hospital his blood pressure was 64/40, pulse 100, respirations 18 per minute. The wounds were explored a few hours after injury under pentothal, nitrous oxide, and ether. Each kidney had been penetrated by the missiles but the abdomen had not been injured.

His vital signs stabilized and his subsequent course was smooth. Bowel sounds were absent for a few hours but returned by the second day after operation. At this time he was given, orally, 100 grams of deuterium oxide mixed with 100 grams of glucose (Fig. 16). After 4 hours, the concentration of deuterium in the gastric fluid had decreased to 3 per cent. His blood sugar rose from 127 mg. per 100 ml. (fasting) to 352 mg. after 45 minutes. After 4 hours only 5 per cent of the glucose could be recovered from the stomach.

Discussion

The studies of the six normal subjects (Figs. 1–6) demonstrate the rapid equilibration of water (deuterium) following its ingestion. Equilibration appears to occur in the normal man within 2 or 3 hours after the ingestion of 100 grams of deuterium oxide, an observation

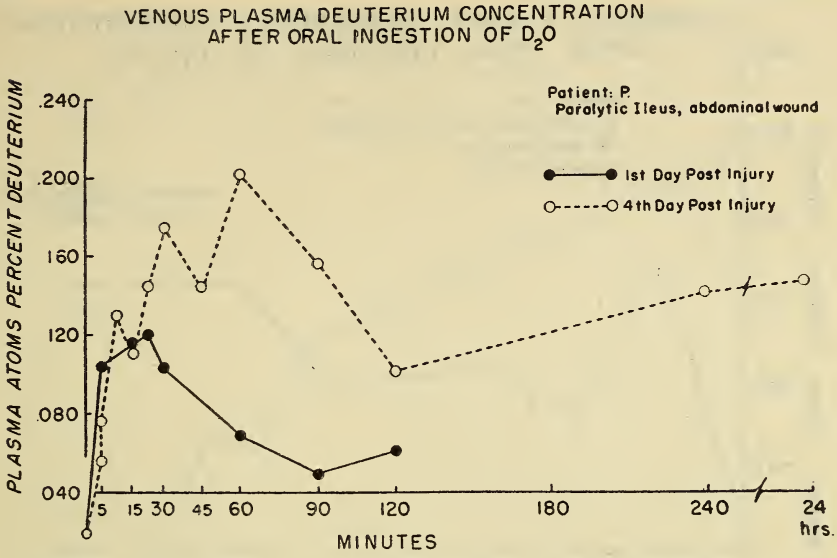

FIGURE 12 (Patient No. 6). This casualty had a severe peritonitis. Equilibration after 2 hours had not been approached on the first day after injury. By the fourth day, there had been a marked clinical improvement as well as an improvement in deuterium absorption. Note, however, that compared with the concentration after 24 hours, equilibration had not been reached after the first 4 hours. Again, a prolonged period is observed during which the deuterium is entering the plasma faster than it is leaving.

Note. In the graph, the deuterium concentration for the second study has been corrected for the residual deuterium from the earlier study.

which confirms this finding in the subject reported by Schloerb and associates.[9] The equilibration curve reflects the effects of peristaltic activity, gastrointestinal absorption, intravascular circulation and diffusion throughout the extracellular and intracellular fluids. The summation of these dynamic processes normally permits equilibration to occur very rapidly.

The study of the first three battle casualties demonstrates, as a preliminary observation, that following rather severe injuries to the chest or extremities, or burns of moderate extent, equilibration is delayed. The delayed rise in venous deuterium concentration in these patients represents a decreased rate of absorption, for when deuterium oxide is given intravenously to the injured man, it leaves the circulation more slowly than in the normal man.[6]

Patient No. 3 (Fig. 9) demonstrates that, 3 hours after injury, the absorption of water was slower than normal. Three days later, the rate of absorption had increased but still was slower than normal. This impairment in absorption is quite definite and unexpectedly prolonged.

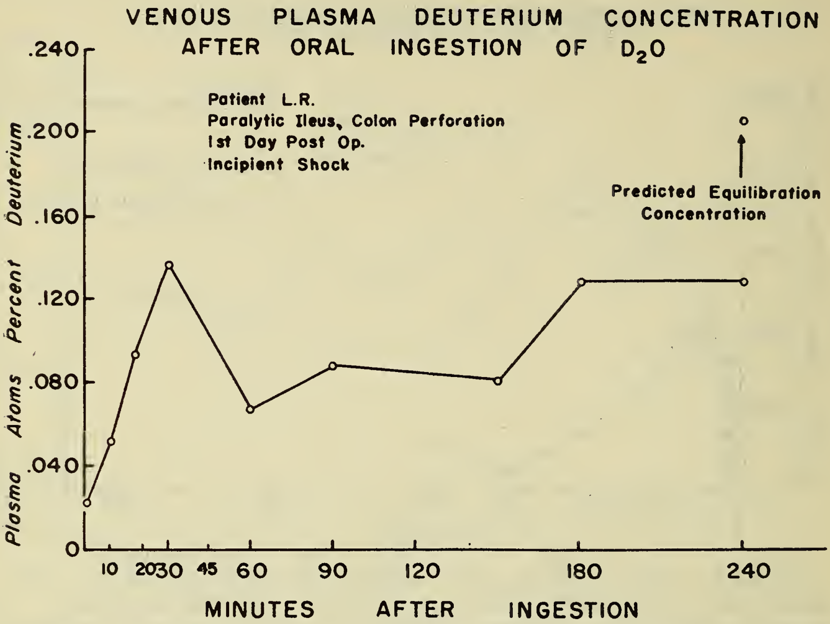

FIGURE 13 (Patient No. 7). This casualty had an unstable circulatory system as well as a marked paralytic ileus. He died the following day with peritonitis. Note that his plasma deuterium concentration after 4 hours was only 60 per cent of the predicted concentration, based on estimate of body water at 63 per cent of body weight. Almost a third of the deuterium was still present in his stomach at the conclusion of the study.

When the study was repeated on the third day, the patient had peristalsis which was normal by auscultation. He had also had a normal bowel movement.

The rapid rise in blood glucose concentration following the ingestion of glucose strongly suggests an active absorption process rather than a process of passive diffusion, for numerous studies have shown that such an active process is normally responsible for the transfer of glucose across the bowel membrane.[2, 3] This observation appears valid in spite of the fact that under these circumstances glycogen deposition is known to be retarded.[1]

Although in these first three casualties the absorption of water did not appear to be normal, the deficiency was not great. All three patients were maintained on oral fluids only and this therapy controlled their thirst and maintained an adequate urinary output. Further study is necessary but these observations, backed by clinical experiences, suggest that most such patients can be treated effectively by the oral administration of water. Certainly, in the treatment of

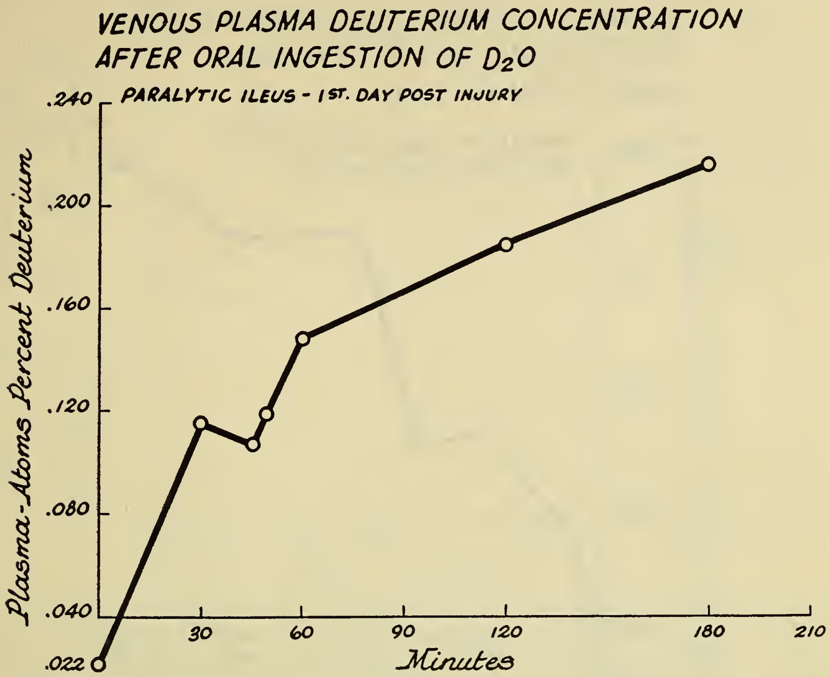

FIGURE 14 (Patient No. 8). Although the plasma deuterium concentration rose steadily for 3 hours, equilibration had not yet been reached.

mass casualties, water must be given orally to such patients unless anesthesia is impending.

Following injury to the abdominal viscera, the delay in absorption and equilibration was often quite marked. When superimposed on injury, hypotension also was associated with a profound deficiency in absorprion (Fig. 10). The deficiency in absorption was present immediately after injury and persisted through the first few days thereafter. Like the function of the kidney,[8] liver [10] and other organs the function of the gastrointestinal tract was slow to return to normal. As with the other organs, the function had not returned to a normal state even when function appeared normal by clinical observations. Thus Patient No. 9 demonstrated a residual deficiency in the absorption of water as late as 7 days after the resumption of daily bowel movements. Absorption was definitely occurring as his stools were formed instead of liquid. The equilibration curve, however, demonstrated a delay.

During the early period after abdominal injuries, peristalsis was usually inaudible. Nevertheless, the occasional peaking in the curve

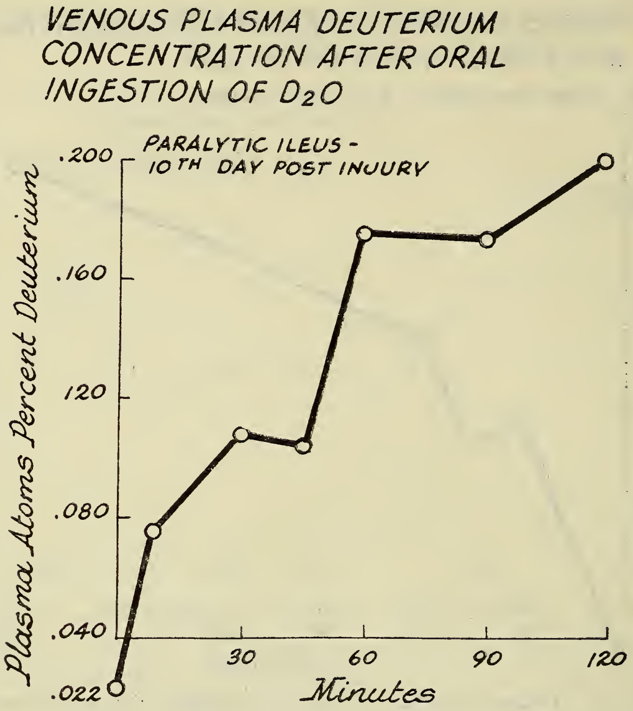

FIGURE 15 (Patient No. 9). This casualty had had a severe abdominal injury with peritonitis. At the time of this study, his gastrointestinal function had been normal, as determined clinically, for 7 days. Note, however, the residual marked delay in absorption of water.

of plasma deuterium concentration (Fig. 10) suggests the activity of intermittent peristalsis and raises the question as to whether the basic defect underlying the slow equilibration is primarily in motility rather than the absorptive process per se. Clinical experience with advanced paralytic ileus, however, has demonstrated numerous instances in which the entire bowel was filled with fluid and a defect in the absorptive process was obvious.

Whatever the underlying mechanism, the soldiers with abdominal injuries absorbed water quite slowly following its oral administration. They often vomited if given water orally in appreciable quantities. Anesthesia and laparotomy had to be performed at the earliest possible time. Motility was reduced and the bowel was often found to be distended with unabsorbed fluids. Thus even under the compromises necessary in the treatment of mass casualties, the oral administration of fluids has no place in the early treatment of patients with major intra-abdominal injuries.

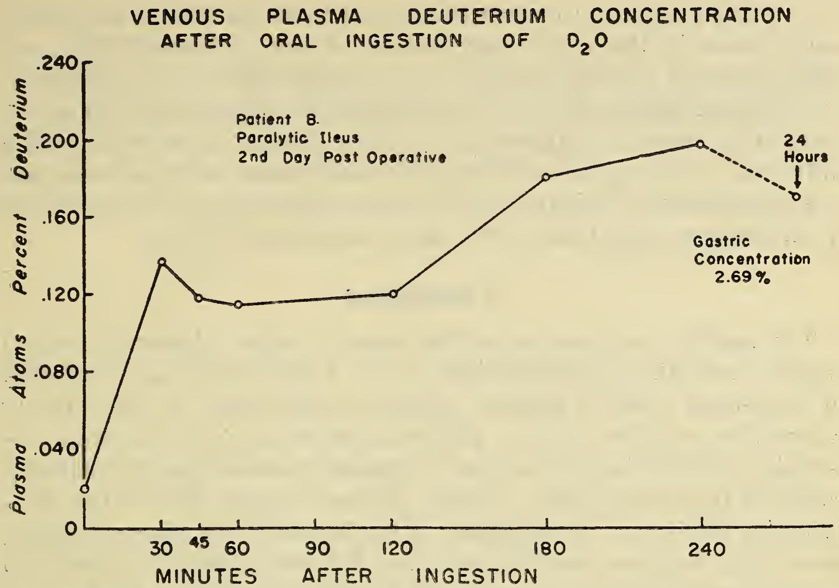

FIGURE 16 (Patient No. 10). This casualty had a wound limited to the kidneys and retroperitoneal area. His clinical course was benign. Peristalsis became clinically detectable on the day of this study. Four hours after ingestion of the deuterium, equilibration was not complete. This casualty had 100 grams of glucose instilled into the stomach with the deuterium oxide (300 ml. total). The glucose tolerance curve was diabetic in form, paralleling the deuterium curve. Four hours after ingestion 5 per cent of the glucose and 3 per cent of the deuterium were recovered from the stomach. This might again suggest an active absorptive function of the gastrointestinal tract at this time.

Summary

1. As measured by deuterium equilibration curves, water rapidly enters the blood from the gastrointestinal tract of the normal man. Equilibration of deuterium throughout the body appears to occur in the normal man within 2 or 3 hours after the ingestion of 100 grams of deuterium oxide.

2. Preliminary studies indicate that, following burns of moderate extent or severe wounds of the chest and extremities, deuterium absorption is impaired but remains much more rapid than after an abdominal injury.

3. Following intra-abdominal injuries, deuterium absorption from the gastrointestinal tract is markedly delayed. This function may still be impaired as late as 10 days after injury and as late as 7 days after the resumption of "clinically normal" gastrointestinal function.

Peripheral vascular collapse due to an intra-abdominal injury is associated with only a negligible absorption of deuterium.

4. The rapid fall in concentration and total amount of deuterium and glucose in the upper gastrointestinal tract following their oral administration and the concurrent rise in blood glucose concentration, as well as in plasma deuterium concentration, suggests that an active absorptive process is functioning rather than a process of simple diffusion. The control of thirst, the solid nature of the stools, and the maintenance of urinary output proves that water is being absorbed in all patients except those with acute abdominal injuries.

Conclusions

The healthy, unwounded soldier absorbs water (deuterium oxide) rapidly from the gastrointestinal tract. Gastrointestinal absorption of deuterium oxide is slightly retarded after injury to the chest or extremities, or after burns. Following intra-abdominal injuries, absorption of deuterium oxide from the gastrointestinal tract is markedly retarded for several days. These studies suggest that in the compromises which may be necessary in the treatment of mass casualties, water may be given orally at any time following injury, if there is no intra-abdominal injury, if anesthesia is not anticipated for the immediate future, and if the casualty is not comatose. Even under conditions in which mass casualties must be treated, oral fluid therapy for the casualties with major abdominal injuries should be avoided during the first few days following injury.

The response of the gastrointestinal tract to severe trauma, like the response of every other system and organ in the body, is a response of tremendous magnitude extending over a long period of time.

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Chapter 3

Studies of the Absorption and Equilibration of Water (Deuterium Oxide) from the Gastrointestinal Tract Following Abdominal Surgery under Spinal Anesthesia*

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and

Captain John H. Davis, MC, USAR

in collaboration with

The Division of Atomic and Radiation Physics

National Bureau of Standards

Washington, D. C.

Schloerb and his co-workers [3] described an equilibration curve in venous blood following the oral ingestion of deuterium oxide (heavy water) in a human subject. They found an equilibration time of approximately 3 hours.

As part of a study of the systemic response to trauma, this observation was confirmed and extended.[1] Similar studies were made in battle casualties who had suffered injuries involving the abdominal viscera. It was found that in such a casualty, equilibration of deuterium oxide from the gastrointestinal tract was markedly slowed. Evidence was presented which suggested that this defect involved an actual decrease in the rate of absorption of water from the bowel. The deficiency was found to persist as long as 7 days following the return of normal gastrointestinal function as measured by clinical observations.

This study of patients undergoing abdominal surgery of the types commonly done in civilian practice is an extension of the work done on battle casualties.

The methods of handling the blood samples and of analyzing the plasma for deuterium have been previously described.[1]

Patient No. 1. This 33-year-old healthy man, after fasting for 12 hours, and while at bed rest, drank 100 grams of deterium oxide. The changing concentration of deuterium in the plasma is demonstrated in Figure 1. Equilibration of the deuterium throughout the body occurred within 90 minutes. Immediately following the uncom-

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*Previously published in *Surgery 36*:1127, 1954.

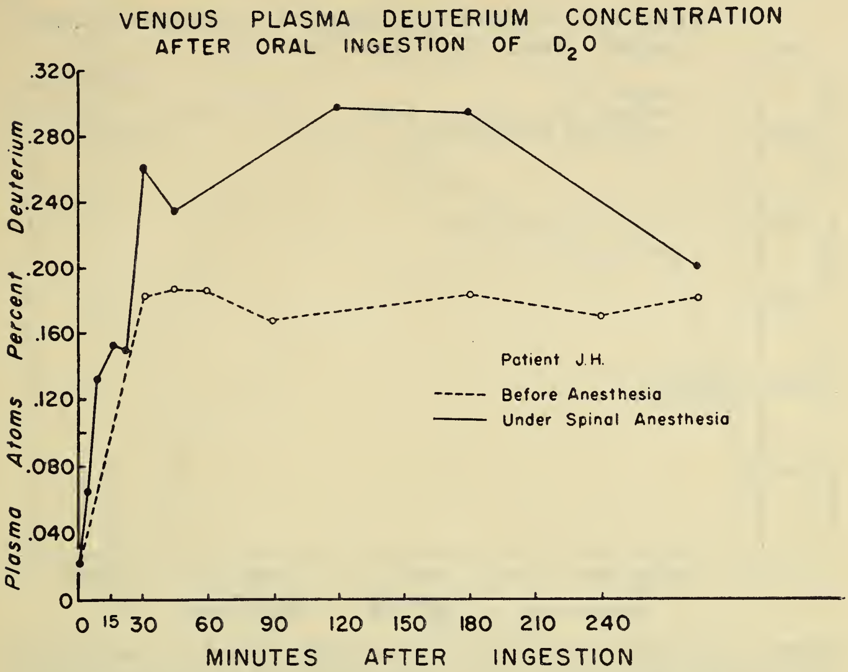

Figure 1. Deuterium equilibration curves before and during spinal anesthesia.

Note. The concentration of deuterium for the second study has been corrected for the residual plasma concentration following the first study.

plicated repair of bilateral indirect inguinal herniae, under spinal (procaine) anesthesia, the study was repeated (Fig. 1). At the time of the second study, the patient was still anesthetized below the level of the eighth intercostal nerve.

The operation required only 60 minutes and involved entering the abdomen only at the time of ligating the peritoneal sac. The bowel was not handled at any time.

Postoperatively, the patient took fluids orally in amounts sufficient to control thirst. There were no gastrointestinal symptoms other than constipation for 72 hours.

Patient No. 2. This 23-year-old soldier entered the hospital after an illness of 2 days' duration. Laparotomy under spinal (procaine) anesthesia revealed a gangrenous appendix, without perforation. Appendectomy, without additional exploration, was performed, requiring 30 minutes.

Immediately after operation, the stomach was emptied and the patient was given 100 grams of deuterium oxide, orally.

The results of the study are demonstrated in Figure 2.

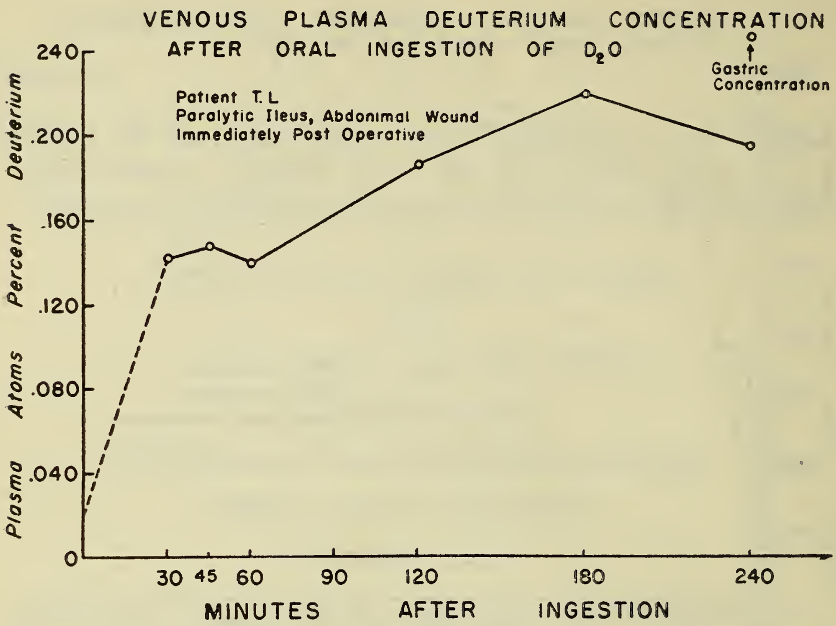

FIGURE 2. The effect of laparotomy and anesthesia resulted in a slower equilibration than seen in Patient No. 1. Equilibration has not been reached within 240 minutes.

Patient No. 3. This 25-year-old soldier was admitted to the hospital with abdominal pain of approximately 48 hours' duration. Laparotomy under spinal anesthesia revealed a perforated appendix with generalized peritonitis. Appendectomy was performed.

On the first postoperative day, 15 hours after operation, his blood pressure was 128/80, pulse 100, oral temperature 99.8°. No peristalsis could be heard. He had received no medication except antibiotics. He was given at this time 100 grams of deuterium oxide orally, his stomach having been emptied previously by means of a gastric tube.

The results of the study are demonstrated in Figure 3.

Fluids were given intravenously for 48 hours. His subsequent course was uneventful.

Patient No. 4. This 22-year-old soldier became ill 4 hours prior to hospitalization. Examination demonstrated an incarcerated inguinal hernia which was immediately repaired under spinal (procaine) anesthesia. The incarcerated small bowel was discolored but was viable.

He was placed on a course of parenteral fluids and gastric suction.

On the first postoperative day he had no audible peristalsis. Twenty-four hours after operation, he was given 100 grams of deuterium oxide orally. He had received no drugs during the previous 18 hours.

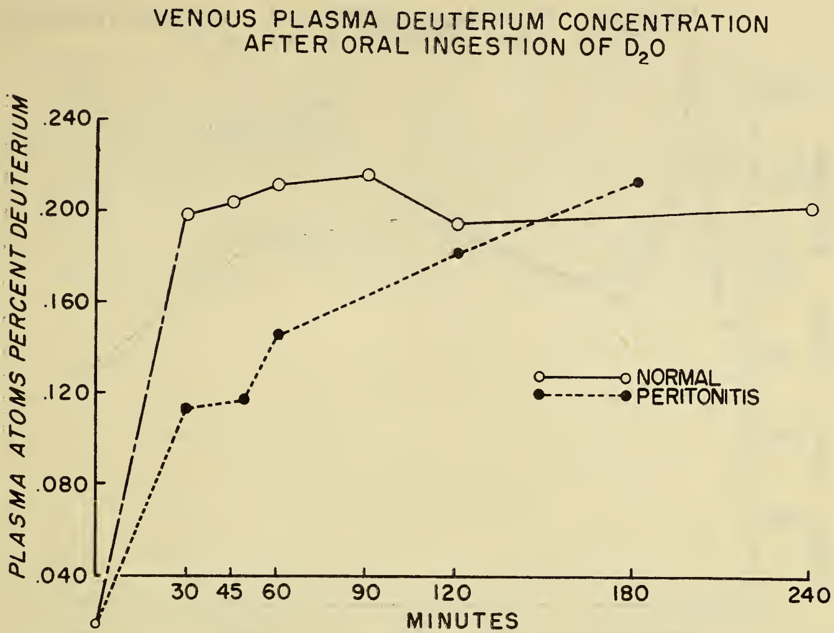

FIGURE 3. The solid line represents a study of a second control subject. Equilibration in Patient No. 3 (dotted line) has not been reached within 180 minutes.

The equilibration curve is demonstrated in Figure 4.

His subsequent course was uncomplicated.

Discussion

All four patients demonstrated a delayed equilibration time following surgery.

Patient No. 1 demonstrated an equilibration time of 90 minutes following the oral ingestion of 100 grams of deuterium oxide. When the study was repeated following herniorrhaphy and while still under spinal anesthesia, the plasma concentration of deuterium rose to greater levels than had been noted during the control study. This increased concentration gradually subsided to the level of equilibration.

This high concentration cannot be explained simply on the basis of splanchnic vasodilatation and increased rate of absorption for deuterium equilibrates rapidly following its intravenous injection.[2], [3] The prolonged period during which the deuterium concentration is elevated must represent a slow diffusion from the blood stream and a continued diffusion or absorption from the gastrointestinal tract during this period.

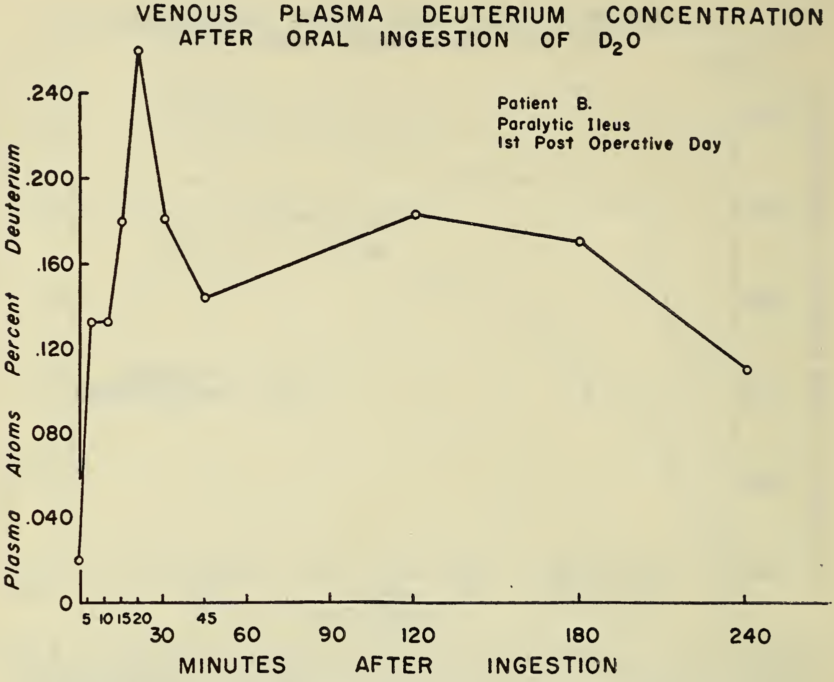

FIGURE 4. Equilibration has not been reached within 240 minutes.

The second patient demonstrated an equilibration curve qualitatively similar to that of the first patient. Both patients were studied immediately following the completion of the operation.

The third patient had a generalized peritonitis. His slowly rising deuterium concentration (Fig. 3) and prolonged equilibration period is similar to the pattern found following intestinal perforations due to combat injuries.[1] The delayed equilibration in this patient was due primarily to the decreased rate of absorption or diffusion from the bowel.

Patient No. 4 had a rapid increase in the plasma deuterium concentration which reached a peak in 20 minutes (Fig. 4) and then subsided. This has been described as occurring in the normal subject.[3] Equilibration, however, was delayed.

Summary

The equilibration time of deuterium oxide, following oral ingestion of 100 grams, was prolonged in four patients who had undergone appendectomy or inguinal herniorrhaphy within the preceding 24 hours. This deficiency appears to be proportional to the magnitude of the original disease or injury.

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Chapter 4

Equilibration Time of Water (Deuterium Oxide) Following Intravenous Injection in the Battle Casualty*

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This study of the equilibration time of water (deuterium oxide) following intravenous injection was part of a broad survey of the systemic response to injury carried out by the Surgical Research Team on the Eastern Front in Korea during 1952–53. The reaction to severe injury appears to involve a response of every organ, every system, and presumably every cell in the body. This response to injury is not a response of a few hours but is of days or weeks in duration.

Following its intravenous injection in the normal subject, deuterium oxide diffuses very rapidly throughout the total body water. Equilibration was found by Schloerb and associates [2] to be complete within 2 hours.

This rate of diffusion may well be a measure of the efficiency of the "total circulation" of the body. It measures the over-all efficiency of the mixing within the blood stream, delivery to various parts of the body, diffusion into extracellular and intracellular fluid, secretion into the gastrointestinal tract and finally equilibration. By measurement of the efficiency of the over-all circulation in this broader sense the status of the circulation may be assayed as to its efficiency in taking substances from one fluid compartment or from one cell to another across several membranes and across several fluid compartments. For example, the circulation must move oxygen from the pulmonary alveoli to the muscles of the leg and metabolites from the cells of the leg to the cells of the liver, kidneys or lungs across several fluid compartments. This activity cannot be evaluated by measure-

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*Previously published in *Surgery, Gynecology and Obstetrics, 99*:703, 1954.

ments of blood pressure, blood volume, cardiac output, or peripheral resistance, but the equilibration rate of intravenously injected deuterium oxide offers a means of testing it.

Material and Methods

The study was done in a Forward Surgical Hospital in Korea. Deuterium oxide (99.8 per cent pure) was prepared as an isotonic solution of sodium chloride. The injection was made by syringe and required approximately 1 minute.

Venous samples were then taken at intervals from the opposite arm. The plasma was separated, placed in a sealed glass test tube and shipped via air to the Bureau of Standards for analysis of deuterium content by a method which has been previously described.[1]

Five battle casualties and two normal subjects were studied.

Observations

Normal Subjects. Two normal male subjects were studied, one 32 years of age (Fig. 1), the other 20 years of age (Fig. 2). Each was given 50 grams of deuterium oxide in the antecubital vein.

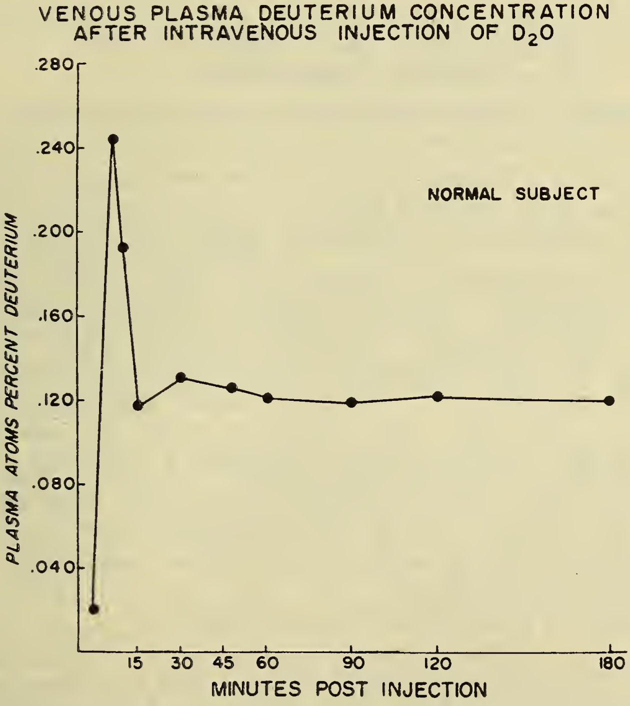

FIGURE 1. Equilibration was very rapid and was complete within 60 minutes.

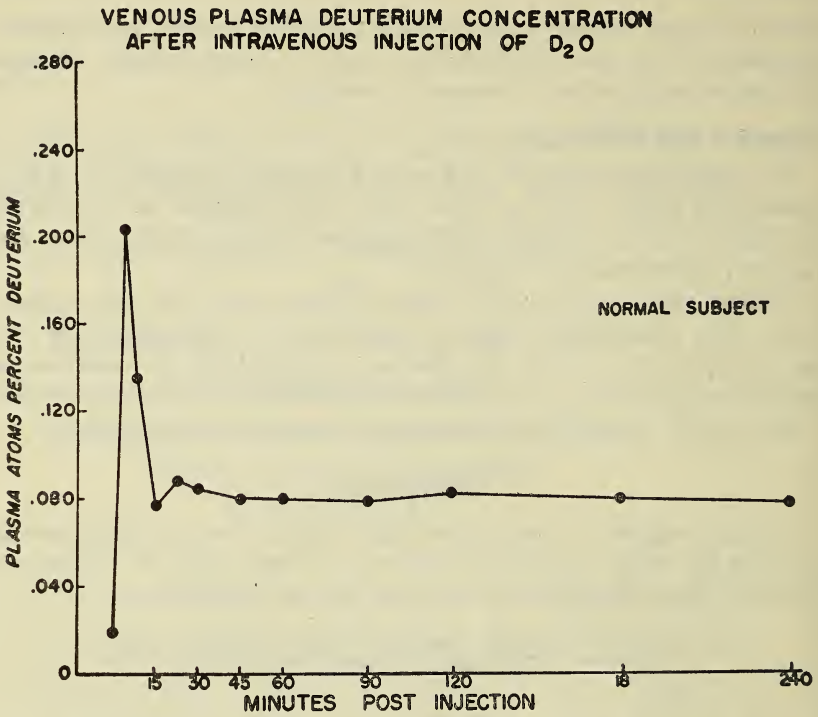

FIGURE 2. Equilibration probably occurred within 45 minutes.

Patient No. 1. This 22-year-old soldier was injured 6 hours prior to admission to the forward hospital. His injury, inflicted by small arms fire consisted of a penetrating wound of the arm. Arterial bleeding was controlled by ligation of a small vessel. The radial pulse was palpable. His blood pressure was 60/20, pulse 120 per minute. After a transfusion of 500 ml. of blood, his blood pressure was 80/50. He was then given a rapid injection of deuterium oxide (50 grams) intravenously. Sixty minutes later transfusion was again started as a slow drip. His subsequent course was smooth. His plasma volume (T–1824 method) indicated a deficiency of 23 per cent of the normal volume calculated as 45 ml. per kilogram of body weight. All studies of deuterium concentration were made from venous plasma from the arm opposite the one used for the infusion of deuterium oxide and blood.

The results of the study are shown in Figure 3.

Patient No. 2. This 31-year-old American soldier was admitted to the forward hospital 5 hours after injury. The wound was produced by artillery shell fragments penetrating the chest, diaphragm and liver. Laparotomy under pentothal, nitrous oxide and ether anes-

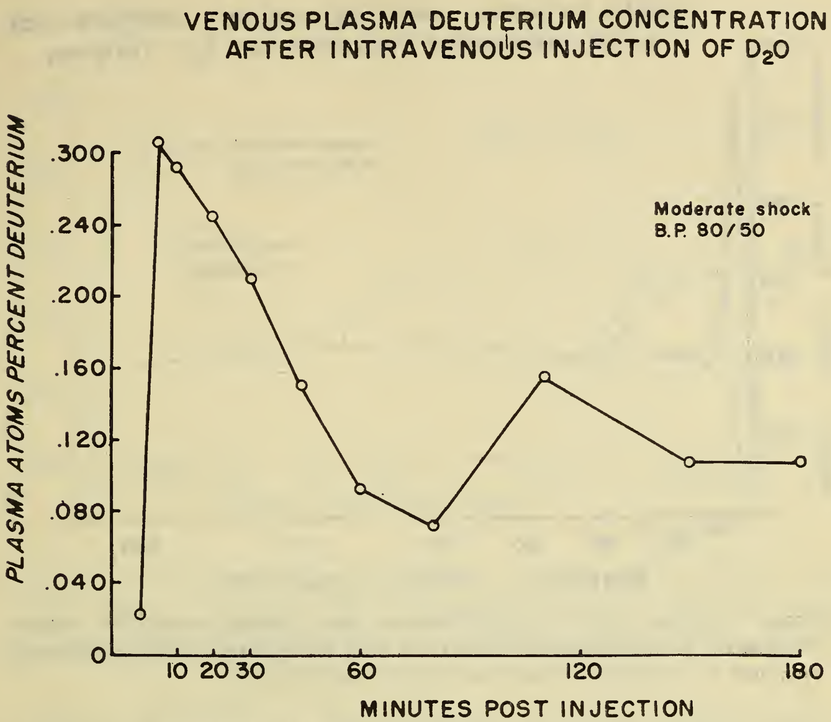

Figure 3 (Patient No. 1). The period of initial elevation of plasma deuterium concentration is quite prolonged and probably indicates a reduction in capillary circulation.

thesia permitted drainage of the small hepatic wound. His subsequent course was very smooth.

On the first day after injury, his plasma volume measurement demonstrated a deficit of 12 per cent but he appeared in excellent condition. His vital signs were normal. At this time he was given 50 grams of deuterium oxide intravenously (Fig. 4). His course remained uneventful.

Patient No. 3. This 20-year-old Korean soldier was injured by mortar shell fragments. The wounds included a perforation of the transverse colon and a penetration of the face. He was slightly hypotensive (blood pressure 100/70) on admission to the hospital. After a transfusion of 1,000 ml. of blood, colostomy was performed under pentothal, nitrous oxide and ether anesthesia. His subsequent course was smooth.

On the second day after injury, his plasma volume deficit was 10 per cent. He was, at this time, given 50 grams of deuterium oxide intravenously (Fig. 5). His blood pressure was 110/75, pulse rate 80, pulse volume full.

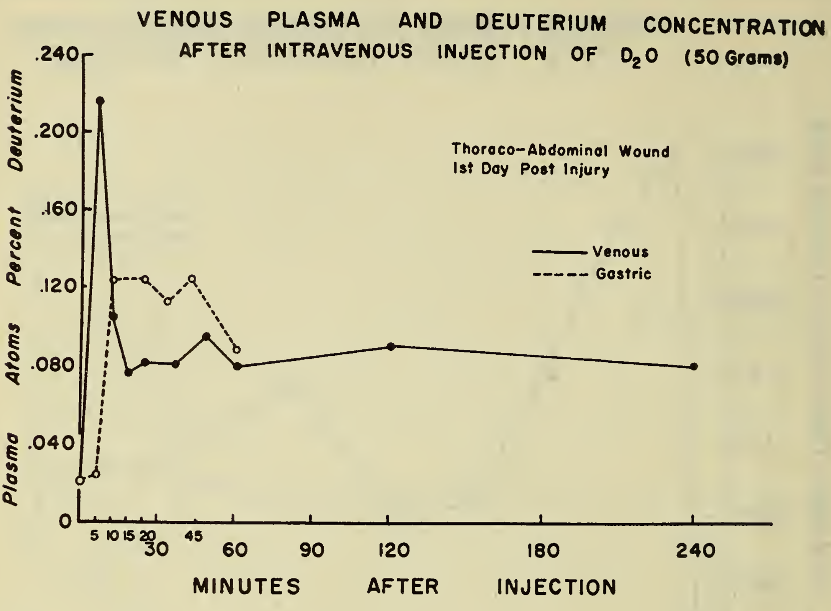

FIGURE 4 (Patient No. 2). Equilibration time appears essentially normal. The gastric deuterium concentration was high immediately after injection and was slow to equilibrate with the venous concentration.

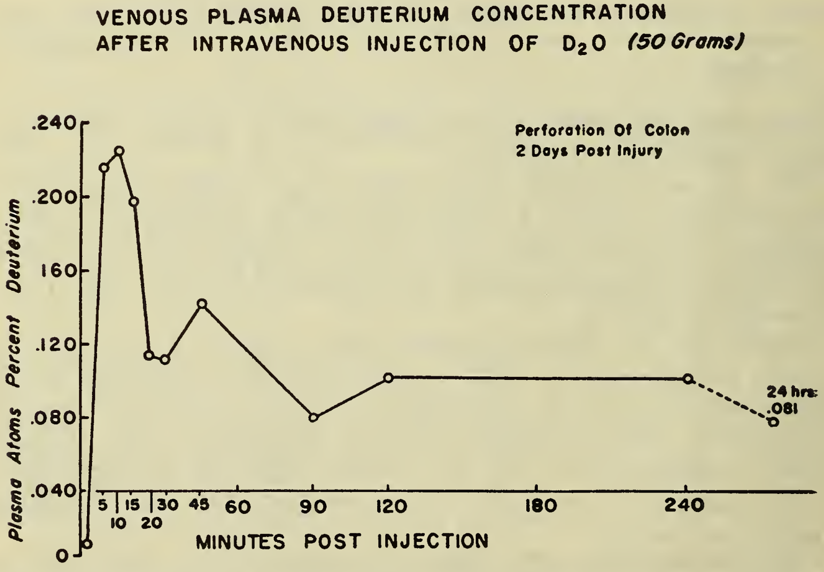

FIGURE 5 (Patient No. 3). The initial rise in concentration is more pronounced and prolonged than in the previous patient. Equilibration again occurred within 2 hours.

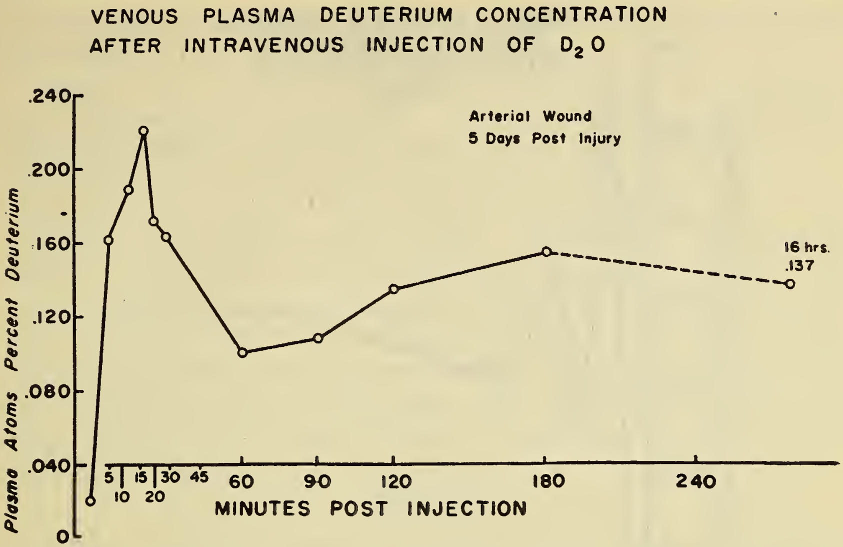

FIGURE 6 (Patient No. 4). Equilibration did not occur within 2 hours. The initial peak in concentration persisted for a prolonged period. These two observations probably result from the marked plasma volume deficiency and the poor circulation in the left leg.

Patients No. 4 and 5. These patients, who were identical twins, were injured on 2 March 1952, by fragments of the same exploding shell. They were admitted to the Forward Surgical Hospital 6 hours after injury.

Patient No. 4 was admitted in a state of incipient shock. His injuries included soft tissue wounds of three extremities. The left femoral artery and vein had been severed and were ligated. The foot became cold and pale and was without a detectable pulse. The capillary circulation was decreased as indicated by a delayed return of color following release of pressure on the skin. Edema was marked. Only after a lapse of several days was the survival of the leg assured.

His postoperative plasma volume determination indicated a deficiency of 24 per cent.

Patient No. 5 had three small wounds of the face and extremities. Débridement was a minor surgical procedure. He was ambulatory immediately after operation. His plasma volume determination indicated a normal volume.

Each patient was given 100 grams of deuterium oxide on the fifth day after injury (Figs. 6, 7).

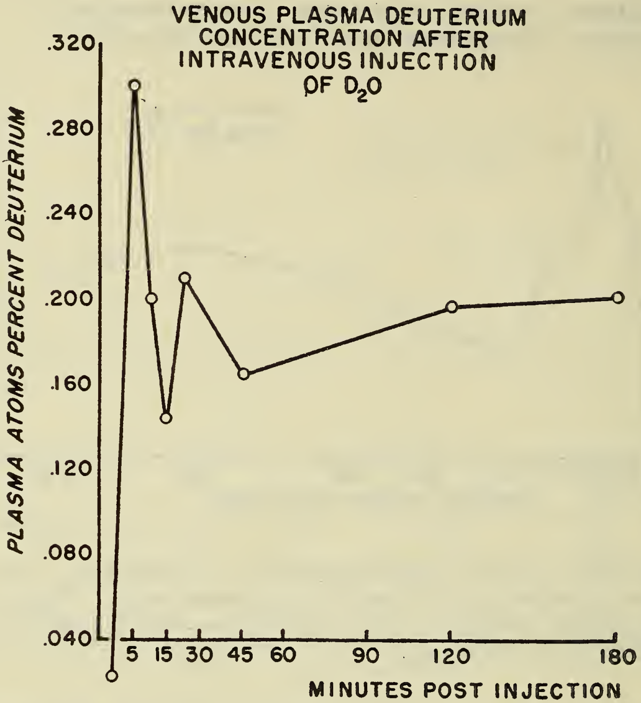

Figure 7 (Patient No. 5). Equilibration has occurred more rapidly and the initial peak in the curve was of shorter duration than in the more severely injured twin. Within the limits of the method, equilibration appears to have been completed within 120 minutes.

Discussion

Following the intravenous injection of 50 grams of deuterium oxide into two normal subjects, a similar equilibration pattern evolved. The venous concentration of deuterium rose sharply but fell immediately so that 15 minutes after the injection the plasma concentration had fallen to a level approximating the concentration of equilibration (Figs. 1 and 2). In both subjects, this initial period of elevation was 15 minutes or less in duration. After minor changes in concentration, equilibration was complete within 60 minutes.

Patient No. 1, who was in a state of moderate hypotension due to blood volume deficiency, demonstrated a sharp rise in deuterium concentration which slowly subsided over a period of 80 minutes. Equilibration was apparently reached after 150 minutes (Fig. 3). This prolonged period of equilibration may well have been the result of blood volume deficiency and vasoconstriction. A reduction in the active capillary bed would decrease the rate of diffusion from the blood to the extravascular fluid compartments. Arteriovenous shunts could also result in such a prolonged equilibration time.

Patient No. 3 required 120 minutes to equilibrate on the second day after perforation of the colon. This deficiency may represent, in part, the effect of the initial injury and, in part, the effect of the continuing nature of the injury in the form of peritonitis.

Patients No. 4 and 5, being identical twins, differed only in the magnitude and nature of their wounds. Patient No. 4 was severely injured and had one extremity with a very limited circulation. His equilibration curve was very similar to that of Patient No. 1 who was hypotensive from blood loss. In contradistinction, Patient No. 5 had an elevated deuterium concentration for only 15 minutes although he did not equilibrate within the first hour. Thus anesthesia and minor injuries affected his circulatory efficiency to a minor degree for a period of at least 5 days.

Summary

1. The equilibration time and pattern of intravenously injected deuterium oxide offers a test of function of the circulation following injury.
2. Equilibration in two normal subjects was almost complete within 15 minutes and was apparently complete within 60 minutes.
3. The hypotensive state following hemorrhage was associated in one patient with a prolonged equilibration time.
4. Severe injury followed by anesthesia was associated with a prolonged deficiency in the circulation as indicated by a prolonged equilibration time of deuterium oxide.

Conclusions

Following severe injuries, the deficiency in the "total body circulation" is quite marked. This deficiency may persist for several days in spite of an apparently smooth convalescence. This defect is presumably due to oligemia and vasoconstriction but this has not been proved.

The response of the circulatory system to severe trauma, like the response of every other system in the body, appears to be of considerable magnitude and to extend over a long period of time.

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Chapter 5

Equilibration Time of Deuterium Oxide Following Subcutaneous or Intramuscular Injection*

(A Study of Korean Battle Casualties)

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Since a previous report [1] demonstrated the limitations of gastrointestinal absorption of water following injury, this study had as its objective to measure the time required for equilibration of deuterium oxide (heavy water) throughout the body following subcutaneous and intramuscular injection and to compare the equilibration time in the normal subject with that in the battle casualty. Such observations might prove of value in planning methods of administration of fluids to mass casualties.

Materials and Methods

The study was carried out in a Forward Surgical Hospital on the Eastern Front in Korea in 1952–1953.

Deuterium oxide (99.8 per cent pure) was given over a period of approximately 1 minute by injection. Venous blood samples were drawn at frequent intervals, the plasma separated and placed in sealed test tubes.

The plasma was then shipped via air to the National Bureau of Standards where analysis was performed as previously described.[1]

Results

Equilibration Time Following Subcutaneous Injection

Normal Subject. The equilibration curve of deuterium oxide following the subcutaneous injection of 50 grams into the lateral thigh of a normal subject is shown in Figure 1. The subject was lying quietly throughout this period. The curve flattens out after 120

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*Previously published in *Surgery 36*:1119, 1954.

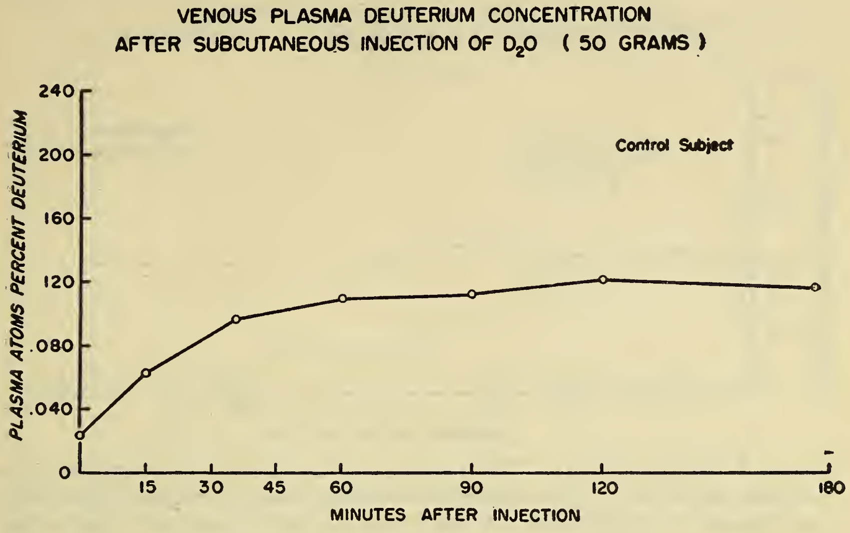

FIGURE 1. The equilibration curve in the normal. Equilibration appears to be complete within 120 minutes.

minutes and equilibration throughout the water of the entire body has probably occurred. This evidently represented, in part, a transfer of water (D_2O) from the thigh into the circulation and thence throughout the body. The belief that this represented an actual transfer of water rather than an exchange of water by diffusion is based on the disappearance of the mass and the resultant disappearance of the discomfort in the thigh. Furthermore, clinical experience has amply demonstrated that fluid, subcutaneously administered, will prevent thirst and maintain urinary output.

The equilibration curve depicted in Figure 1 is similar to the curve reported by Schloerb and his associates [2] although the latter described a more prolonged equilibration time following the administration of deuterium oxide over a longer period of time.

Battle Casualties. The equilibration time following subcutaneous injection was studied in four battle casualties. Three were selected on the basis that they could not, at this early time, take fluids orally due to the nature of their injuries (bowel, brain and cervical spinal cord). The fourth patient had received an injury to the extremity and could have tolerated fluids orally.

Patient No. 1. This Korean soldier was injured by shell fragments at 1800 hours on 22 March 1952. The fragments penetrated the right side of the neck and the spinal cord in the cervical region. On admission to the hospital, by ambulance, 24 hours later, his blood

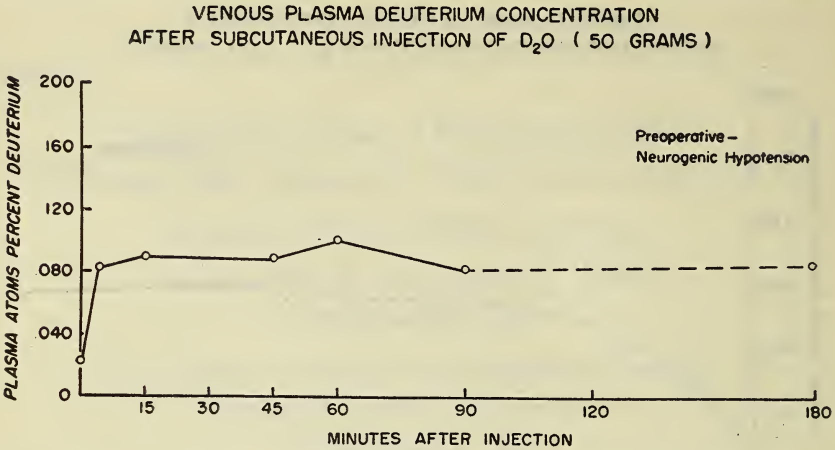

FIGURE 2 (Patient No. 1). This patient had an incomplete severance of the cervical spinal cord. The venous concentration rose very rapidly, presumably as a result of redistribution of blood flow following spinal cord destruction.

pressure was unobtainable. His pulse was barely palpable. He had not lost a significant amount of blood. His blood pressure did not respond to the intravenous administration of neosynephrine. After a transfusion of 1,000 ml. of blood, he was given subcutaneously 100 gm. of deuterium oxide into the lateral tissues of the thigh. His equilibration curve is demonstrated in Figure 2.

He died 8 hours later. Autopsy revealed an incomplete severance of the cervical spinal cord.

Patient No. 2. This 20-year-old South Korean soldier was wounded by mortar shell fragments on 28 January 1952. He was slightly hypotensive when admitted to the forward hospital. His blood pressure was 100/70 but responded to a transfusion of 500 ml. of blood. He was then given a subcutaneous injection of 50 gm. of deuterium oxide into the lateral aspect of the thigh. His equilibration curve is demonstrated in Figure 3.

Subsequently, the patient was found to have a perforation of the transverse colon which was exteriorized. His postoperative course was smooth.

Patient No. 3. This 20-year-old American soldier was wounded at an unknown hour on 21 February 1952 by artillery shell fragments. The fragments perforated the skull in four or five places and produced an extrusion of the cerebral cortex. He was admitted to the forward hospital by Marine helicopter on the same day. His blood pressure was 140/90, pulse 64, respiration 24. He was unconscious and his pupils were dilated and fixed. He was considered inoperable. Three hours after admission he was given an injection of 100 gm. of deu-

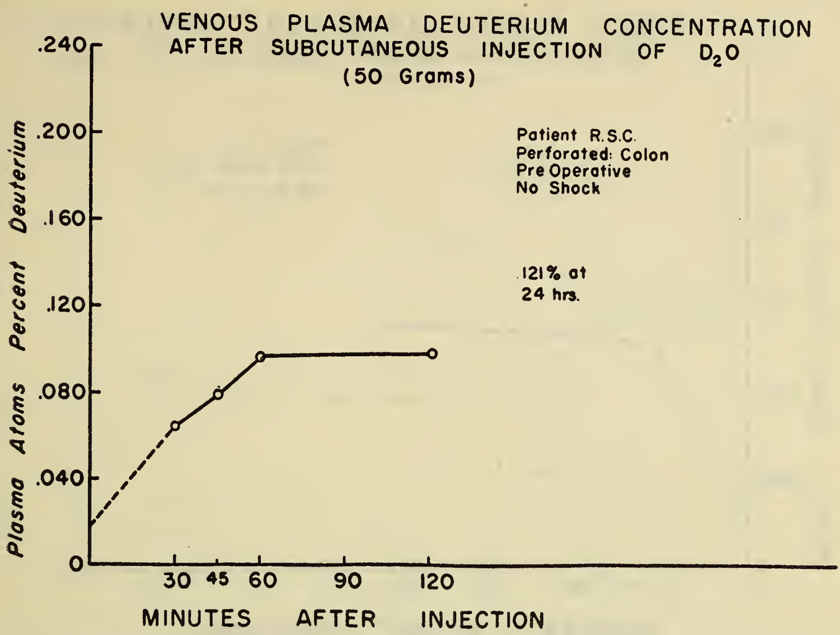

FIGURE 3 (Patient No. 2). The plasma concentration of deuterium after 24 hours was high, indicating that equilibration was incomplete at the end of 2 hours.

terium oxide into the lateral subcutaneous tissues of the thigh. During the subsequent period of observation, his pressure gradually fell to 60/50. He died shortly thereafter.

The equilibration curve of deuterium in the venous plasma is demonstrated in Figure 4.

Patient No. 4. This 22-year-old American soldier received a perforating wound of the knee at 1900 hours, 28 January 1952. His blood pressure 1 hour later, on admission to the forward hospital, was 80/40. Following a single 500 ml. transfusion, his pressure rose to 110 mm. systolic. He was then given a subcutaneous injection of 50 gm. of deuterium oxide into the lateral aspect of his unwounded thigh. The equilibration curve is depicted in Figure 5.

His wound was subsequently débrided. At the time of evacuation, he appeared in excellent condition.

Equilibration Time Following Intramuscular Injection

Normal Subjects. Two normal subjects were each given 100 gm. of deuterium oxide intramuscularly into the lateral thigh. This was given by injection within a period of 1 minute. During a subsequent period 1 to 2 months later, the study was repeated but to the deuterium

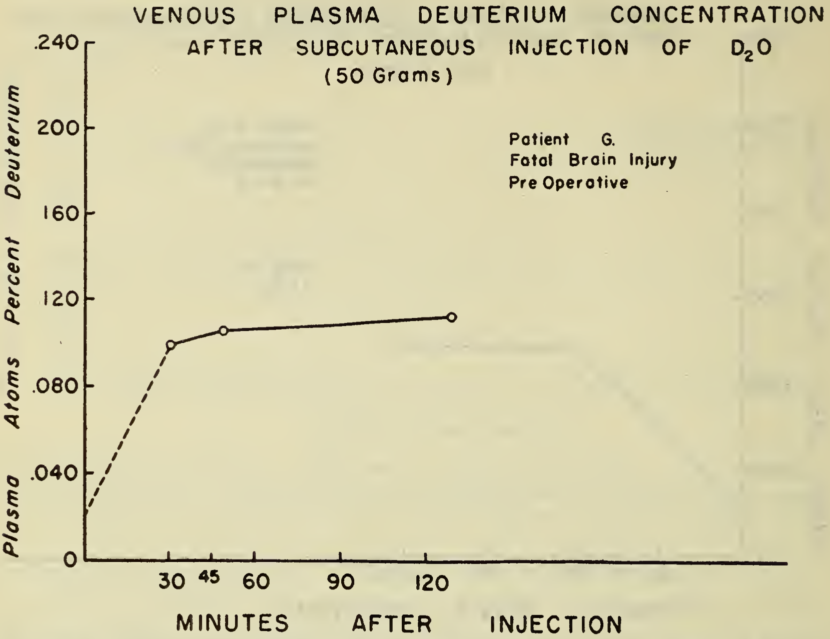

Figure 4 (Patient No. 3). This casualty, with a fatal brain wound and resultant neurogenic hypotension, had a rapid equilibration time similar to Patient No. 1 with the spinal cord injury. A postmortem plasma sample taken at the time of death, 3 hours after the above study, demonstrated a deuterium concentration of 0.110 atom per cent.

oxide was added 150 turbidity units of hyaluronidase. The equilibration curves with the comparative studies are demonstrated in Figures 6 and 7.

Patient No. 5. This 22-year-old Turkish soldier was wounded at 1645 hours 15 May 1952 when he stepped on a land mine. His injuries included a traumatic amputation of the right leg at the calf and multiple penetrating wounds of the left thigh. On arrival at the hospital by helicopter 2 hours later, his blood pressure was 90/50. He was given 500 ml. of blood and his pressure rose to 130/90.

He was then given 100 gm. of deuterium oxide by intramuscular injection into the right thigh. The equilibration curve is demonstrated in Figure 8.

The right leg was subsequently amputated at the calf. His further course was smooth.

Patient No. 6. This 23-year-old American soldier was wounded at 1645 hours, 16 May 1952, by mortar shell fragments. He suffered a trumatic amputation of the right lower leg, along with penetrating wounds of the right thigh. He arrived via helicopter at the forward

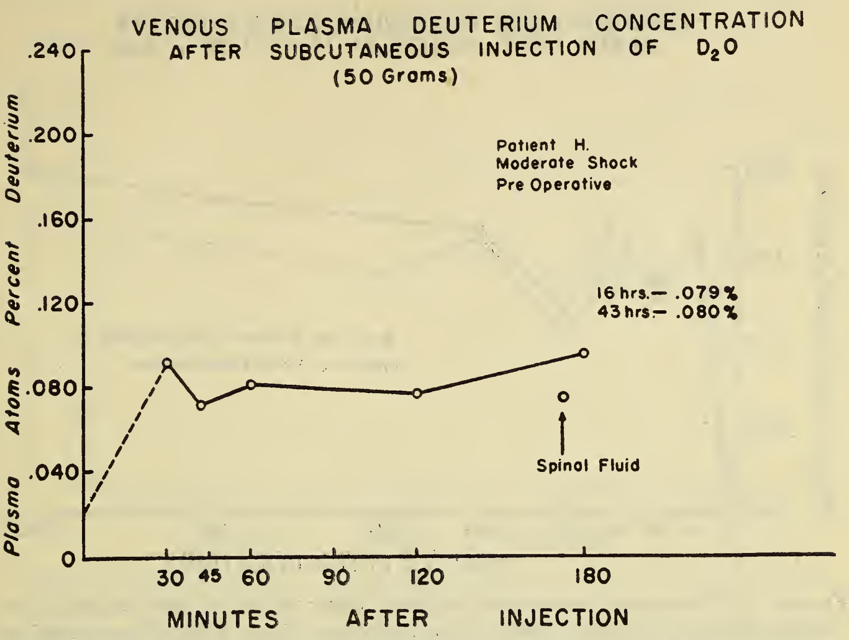

Figure 5 (Patient No. 4). Equilibration has not been reached after 3 hours in this soldier with a rather severe wound of the opposite leg.

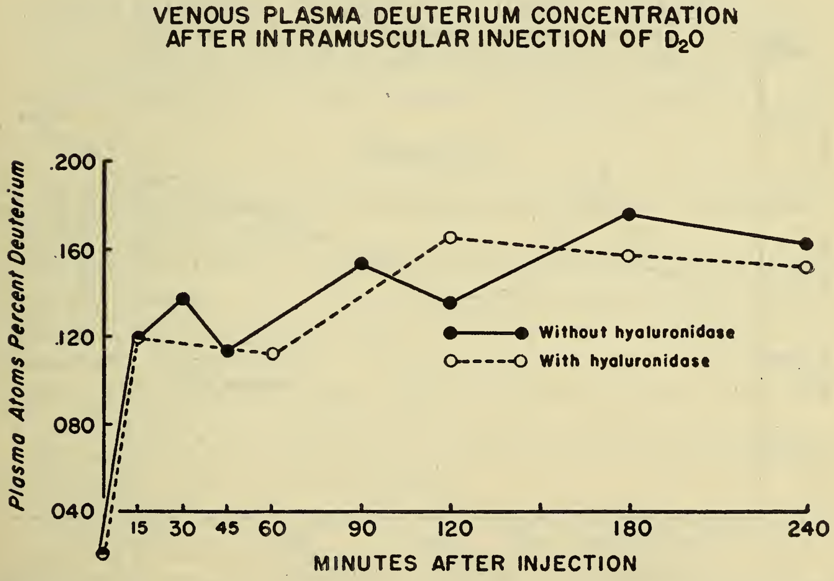

Figure 6. Equilibration has been achieved within 180 minutes in both studies. There is suggestive evidence of an effect of hyaluronidase but this is indefinite. Note that in the graph a correction has been made for the residual deuterium from the first study.

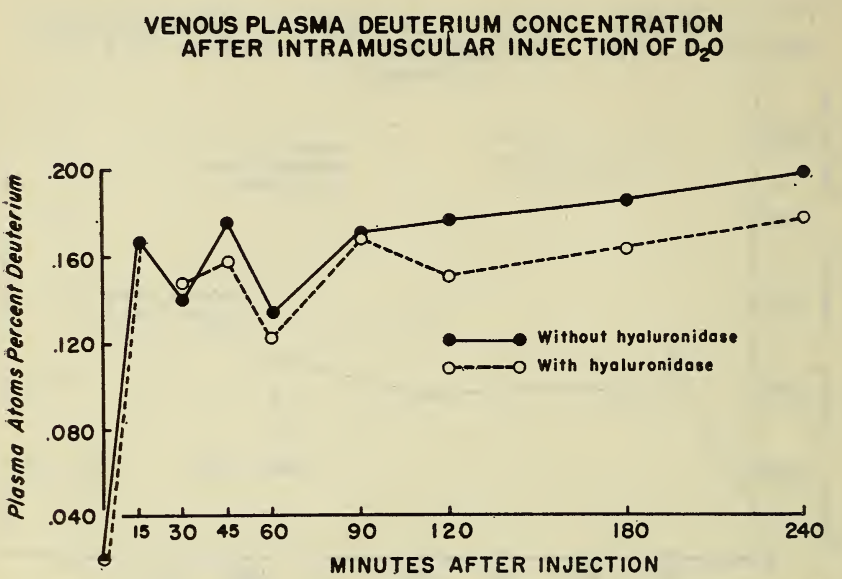

FIGURE 7. Subsequent specimens indicated equilibration after 4 hours. Hyaluronidase did not affect the equilibration time. As in Figure 6, a correction has been made for the residual deuterium concentration in the second study.

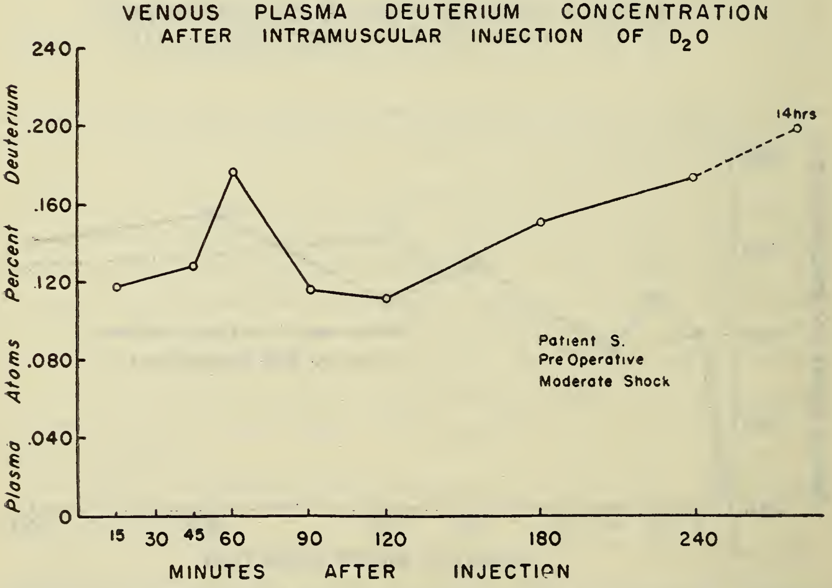

FIGURE 8 (Patient No. 5). Equilibration was very slow and may reflect, in part, a decrease in circulation in the thigh following injuries distal to the area of study.

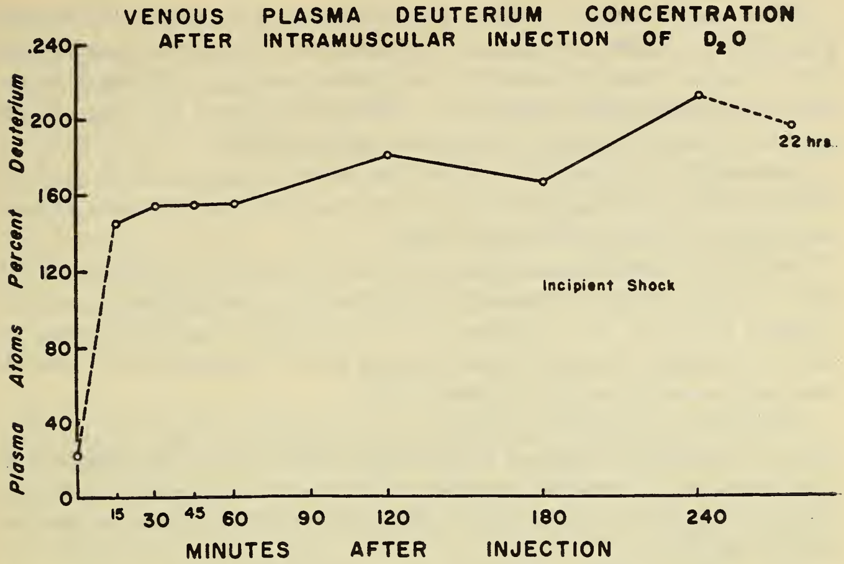

FIGURE 9 (Patient No. 6). The highest plasma deuterium concentration was reached within 4 hours. This patient had wounds similar to those of the previous patient except that in this patient there was no injury to the extremity in which the deuterium was injected.

hospital 2 hours later. His blood pressure was 130/80, pulse 120. He appeared hard hit and was immediately given 1,500 ml. of blood.

Ninety grams of deutuerium oxide was injected intramuscularly into the left thigh (Fig. 9). His subsequent course was smooth.

Discussion

Equilibration following subcutaneous injection in a normal subject occurred within 2 hours.

Patient No. 1 and Patient No. 3 had severe injuries to the central nervous system. The venous deuterium concentration rose very rapidly following subcutaneous injection and equilibration was apparently reached rapidly. This was probably the result of injury to the central nervous system with a resultant increase in blood flow to the skin and subcutaneous tissues.

Patient No. 2 and Patient No. 4, with wounds of the colon and leg respectively, were slow to equilibrate.

Patients with cerebral injuries often cannot take fluids orally because they may be comatose and may aspirate water or vomitus. They do not usually require intensive fluid therapy; yet, under conditions of mass casualties, they may have to wait hours for operation and then for adequate postoperative care.

When compromises in fluid therapy have to be made, this group probably offers the best opportunity for the subcutaneous administration of fluid. Such a method is less time consuming and requires less skill on the part of the attendant. Within the limits of this study, it appears most promising in this group of casualties.

Conversely, the previous study [1] has shown that casualties such as Patient No. 4 with injuries of the extremity can tolerate and absorb water from the gastrointestinal tract.

Patients with abdominal injuries do not tolerate nor absorb well the fluids taken orally. Similarly, equilibration time following subcutaneous injection was prolonged in Patient No. 2 and this route of administration has many disadvantages in the management of casualties with gastrointestinal injuries.

Equilibration following intramuscular injection occurred in 3 to 4 hours. This did not appear appreciably influenced by the addition of hyaluronidase. Perhaps, however, the force of the injection acted as a spreading factor, accounting for the fact that hyaluronidase had no further benefit.

In six other studies, a bottle of saline (1,000 ml.) was placed at a height of 3 feet above the patient. The time required for intramuscular infusion (three subjects) and subcutaneous infusion (three subjects) into the thigh averaged 3 hours and was quite painful. The study was then repeated in the opposite thigh but hyaluronidase (150 turbidity units) was added to each bottle. The average time of infusion was 45 minutes and the discomfort was minimal. Under similar circumstances, hyaluronidase would doubtless speed up the equilibration of deuterium.

Patients No. 5 and 6 who had wounds of the extremities demonstrated a slight to marked slowing of equilibration.

The studies on Patient No. 5 suggested the possibility of a reduced blood flow in the muscles of the thigh proximal to a severe injury of the leg. This remains in doubt; knowledge is needed concerning the changes in the circulation in and around major wounds.

Summary

1. In this preliminary study, the equilibration time following the subcutaneous injection into the thigh of 50 gm. of dueterium oxide was 120 minutes;

2. Following injury to the central nervous system, equilibration time following subcutaneous injection into the thigh was shortened. Two other patients with injuries of the abdomen and leg respectively demonstrated a prolonged equilibration time.

3. The equilibration time following the intramuscular injection into the thigh of 100 gm. of deuterium oxide was 3 to 4 hours. This time was not appreciably changed by the addition of hyaluronidase.

4. Following injury, two patients demonstrated a moderate delay in equilibration following intramuscular injection of deuterium oxide.

5. In the treatment of mass casualties, subcutaneous fluid administration would probably prove useful as an adjunct to therapy of the neurosurgical patients. Hyaluronidase speeds the infusion and lessens the discomfort. Although it did not appear to hasten equilibration under the conditions of this study, it may well prove effective when added to a gravity infusion.

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2. Schloerb, P. R., Friis-Hansen, B. J., Edelman, I. S., Solomon, A. K., and Moore, F. D.: The Measurement of Total Body Water in the Human Subject by Deuterium Oxide Dilution. J. Clin. Invest. *29:*1296, 1950.

Chapter 6

The Hematologic Response to Wounding and to Resuscitation Accomplished by Large Transfusions of Stored Blood*

A Study of Battle Casualties in Korea

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Captain John M. Howard, MC, USAR

This study was undertaken by the Surgical Research Team of the United States Army in order to evaluate present methods of blood transfusion as practiced by American surgical teams at the forward hospitals in Korea. Our military surgeons have become increasingly bold in the use of blood for resuscitation of casualties. Thirty pints of blood and even more may be transfused into a seriously wounded man during the few hours required for his resuscitation and surgery. As a consequence it has been possible to save the lives of many casualties who previously might have died of irreversible shock. Use of such large amounts of blood is, of course, not without its hazards. These hazards would at first glance seem to be compounded by the fact that most of the blood used in the wounded men is collected in the United States and transported by air to Korea. Most of it is 10 to 20 days old before it is used. It is discarded after 21 days. All of the blood is from universal donors. That is to say, it is group O, Rh positive, and is used without cross matching regardless of the blood group of the recipient.

The present study was undertaken to determine what, if any, are the harmful effects of massive transfusions and to learn if the age of the blood and the difference of blood group contribute anything deleterious. Insofar as we were able to tell, they did not. Even after large, rapid transfusions the plasma potassium was rarely elevated and pathogenic amounts of plasma hemoglobin were not encountered. The use of O blood in A recipients undoubtedly resulted in some loss of recipient red cells, as will be shown, but there was no evidence of clinical transfusion reactions.

The hematologic response of these men to transfusion could not be separated from the effects of the wounds that required the transfusion. This report, therefore, is more a study of patients than of transfusions.

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*Previously published in *Blood, The Journal of Hematology 9:*439, 1954.

Materials and Methods

The technical work was carried out by one of us (WHC) in the laboratory of the Surgical Research Team attached to the 46th Army Surgical Hospital in Korea, from late October 1952 until mid-January 1953. The hospital was located several miles behind the infantry division that it supported. Patients were brought by ambulance or helicopter from the battalion aid stations on the line. They were usually received within several hours after they had been wounded. Often they had received transfusions of whole blood or plasma substitutes at medical stations along the line of evacuation. All of the patients were young, their ages ranging from 18 to 24. The average was about 20.5 years. The group included Caucasians, Negroes, Nisei, Puerto Ricans, and South Koreans. Our study involved 37 patients, each of whom was so severely injured as to require blood transfusion. None of the patients had been burned. The size of the transfusions varied from 2 pints to 42. Eighteen of the patients were given 9 pints or more. Because the Ashby studies were especially valuable, we tended to select patients of other than group O. A battery of hematologic studies was carried out on each patient. In most cases the observations were performed serially and were terminated when the patient's condition permitted further evacuation. During the period of the study 1,620 pints of blood were used at the hospital. No hemoglobinuric reactions occurred.

The hematocrit of heparinized blood was measured in Wintrobe tubes, filled at the bedside and centrifuged at 2,000 g for 35 minutes. Red cell counts were done by the method of Dacie[11] in which 20 cu. mm. of whole blood were diluted in 5 ml. of normal saline (1:250). After thorough mixing the cells were counted in a standard counting chamber. Differential agglutination (the Ashby technic) was carried out by pipeting 0.3 ml. of the above red cell suspension into a small test tube containing an estimated 5 mg. of dried anti-A or anti-B serum (Michael Reese). This caused agglutination of the patient's own red cells but did not agglutinate the transfused group O cells. After 30 minutes the tube was centrifuged, the unagglutinated cells were resuspended and counted in a counting chamber.[17] Baseline inagglutinable counts were not always possible because of transfusions given to patients before arrival at the hospital. Where baselines were possible, the count varied between 7,000 and 15,000 per cu. mm. In making the total red cell counts and Ashby counts at least 1,500 cells were counted; where the two values were almost equal at least 3,000 cells were counted. The Ashby counts were of value to establish the ratio of donor (group O) red cells to native (A, B, or AB) red cells after transfusion. Serial Ashby counts revealed alterations of the ratio. An increase of agglutinable native red cells suggested a loss of transfused cells. An increase of inagglutinable group O cells suggested a loss of native cells. Under normal conditions transfused cells are replaced by newly generated native cells at the rate of 0.85 per cent per day.[17]

White cell counts were performed in the usual way. Platelet counts were carried out by the direct method of Brecher and Cronkite.[4] The normal range is 200,000 to 300,000 per cu. mm. Reticulocytes were counted on a dried smear of blood that had been mixed with a saline solution of new methylene blue, as described by Brecher.[3] Normal reticulocyte counts were usually about 0.6 per cent. The method for plasma hemoglobin, described elsewhere,[10] was modified to use benzidine base rather than benzidine dihydrochloride as the indicator. The results were read on a Coleman Jr. spectrophotometer at 515μ. Because an aqueous solution of benzidine was employed these results are probably about 30 per cent low.[6] Normal plasma hemoglobin is less than 5 mg. per 100 ml. of plasma. The plasma hemoglobin of bank blood was determined from specimens of the blood obtained just as transfusions were started, after the red cells had been resuspended in the plasma.

The plasma of transfused O blood carries anti-A and anti-B antibodies into the recipient. It was of interest to learn if, after large transfusions of O blood, the presence of foreign antibodies could be detected in the plasma of recipients who were A, B, or AB. Cold and warm agglutinin titers were measured in serum or lightly heparinized plasma. There was little or no difference in titer when serum and plasma were tested at the same time. Serum was doubly diluted with saline and mixed with an equal volume of a 2 per cent suspension of red cells in saline to give final dilutions of 1:2, 1:4, etc. The test was carried out against group O cells as well as group A or B. Clumping of the O cells indicated nonspecific agglutination. When the titer was higher against A or B cells than against O cells, the difference was taken to represent the titer of specific anti-A or anti-B agglutinins. The tubes were refrigerated for 1 hour at 5° C., centrifuged for 1 minute at 400 rpm and chilled again for 5 minutes before they were shaken and read. Agglutination was rated from 1 to 4 plus. One plus was small but definite clumps; at 4 plus all red cells were clumped in one or two masses. The suspensions were also examined at 37° C. Details of these procedures are described elsewhere.[8] The direct Coombs test for incomplete adsorbed antibodies was performed according to Dacie's instructions.[11]

Table 1. The Circulating Red Cells after Transfusion of Group O Blood

Patient	Blood Group	Transfusion		Day Postoperative	Total RBC Million/ cu. mm.	Inagglutinable RBC Million/ cu. mm.	Proportion of Donor RBC % of Total	Hct	MCV cu. μ	Anti-A Cold Agglutinin
		Size (Pints)	Age (Days)							
A	A	9	14–16	0 Postop	6. 66	4. 27	64	55	83	Tr at 1:8
Multiple lacerations of intestine				1	5. 75	3. 59	62	48	83	
				3	5. 25	3. 40	65	41	78	0
				5	5. 21	3. 47	67	44	84	0
				10	5. 10	3. 34	67	44	88	0
P	A	6	11	0 Preop	4. 70	(14, 000)	0	39	83	0
				0 Postop	4. 71	2. 41	51	45	95	1:8
Massive wound of buttocks and lower back, laceration of rectum				1	4. 43	2. 50	56	36	81	
				3	3. 67	1. 90	52	30	82	1:4
				6	2. 86	1. 23	43	24	84	0
				8	3. 08	1. 27	41	26	84	0
M	A	9	10	0 Preop	3. 60	(7, 000)	0	29	81	0
				0 Postop	4. 53	2. 68	59	38	84	1:4
Penetrating wound of right chest, diaphragm and liver				1	4. 85	2. 97	61	41	85	1:2
				2	4. 40	2. 42	55	34	77	0
				3	4. 39	2. 34	53	34	78	0
				4	4. 02	2. 23	55	32	80	0
H	A	8	11	0 Postop	4. 93	2. 13	43	46	93	trace
Penetrating wound of right chest, lung, diaphragm and liver				1	5. 77	2. 24	39	46	80	0
				5	5. 05	1. 78	35	42	83	0
				10	5. 10	1. 64	32	43	84	0

Table 1. The Circulating Red Cells after Transfusion of Group O Blood—Continued

Patient	Blood Group	Transfusion		Day Postoperative	Total RBC Million/cu. mm.	Inagglutinable RBC Million/cu. mm.	Proportion of Donor RBC % of Total	Hct	MCV cu. μ	Anti-A Cold Agglutinin
		Size (Pints)	Age (Days)							
G	A	8	17	0 Postop	4. 38	3. 39	77	39	89	1:32
				1	4. 34	3. 17	73	39	90	
Multiple wounds of legs with section of right femoral artery				2	4. 77	3. 46	73	41	86	1:16
				4	4. 37	3. 15	72	38	87	
				6	4. 24	2. 75	65	35	83	
				9	4. 38	2. 74	63	36	82	1:4
				11	4. 34	2. 53	58	37	85	1:2
I	A	13	13	0 Aid station	5. 65	(11, 500)	0			0
Penetrating wound of abdomen. Died 30 hrs. postop.				0 Postop	7. 01	4. 72	67	59	84	0
				8 hrs	7. 20	4. 81	67	65	90	
				1	5. 90	3. 93	67	53	90	
				0 Preop	6. 50			46	71	
K	A	7	12–14	0 Postop	5. 06	2. 91	58	46	91	tr
Bilat. fracture of femur				1	4. 71	2. 67	57	38	81	0
II	A	6	11	0 Postop	5. 09	2. 82	55			
Right chest, arm, thigh				2	4. 70	2. 75	58	39	83	
				0 Preop	5. 37			41	76	
E	A	8	12	0 Postop	5. 38	3. 14	58	47	87. 5	0
Multiple wounds including chest				1	4. 64	2. 69	58	37	80	
				10	3. 99	1. 79	45	34	85	
Q	A	6	13	1	4. 53	3. 25	72	38	84	0
Amputation R foot										

U	A	4	12	0 Postop	6. 4	1. 82	35	51	80	0
Thigh, abdomen				1	5. 82	1. 57	37	47	81	0
V	A	3	10	0 Preop	4. 28	(5, 500)	0	35	82	0
				0 Postop	4. 21	1. 71	24. 5	38	90	
Multiple wounds of extremities				1	4. 85	1. 83	26. 5	38	78	0
				2	4. 30	1. 50	28. 5	33	77	0
				4	3. 54	1. 27	28	30	85	0
				5	3. 41	1. 23	28	28	82	0
J	A	2	13	0 Postop	4. 74	0. 90	19	38	80	0
Amputation L foot				1	4. 36	0. 97	22	38. 5	88	0
N	A	2	11	1	4. 85	0. 98	20			tr at 1:8
Multiple light wounds										
O	A	2	9–11	1	5. 29	1. 22	23	40	76	0
Face and skull										
R	B	2	9	1	5. 58	0. 96	17	48	86	0
Multiple light wounds										
T	AB	2	16	1	3. 90	0. 90	23	30	77	Anti B-O
Multiple light wounds										Anti A tr at 1:8

Results

The Bank Blood

The plasma hemoglobin determinations performed on 300 pints of bank blood revealed an average of 34 mg. of hemoglobin per 100 ml. of plasma. In 3 per cent of the bottles the plasma hemoglobin exceeded 100 mg. In 84 per cent the plasma hemoglobin was less than 50 mg. As the blood aged, the plasma hemoglobin gradually increased. At 10 days the average was about 25 mg. per 100 ml.; at 20 days it was about 50 mg. In blood carefully drawn into ACD solution at our hospital, the plasma hemoglobin was 5 to 6 mg. The plasma hemoglobin of heparinized normal blood drawn into an oiled syringe is usually 2 to 3 mg.[10]

The post-transfusion survival of bank blood was studied by means of the Ashby technic of differential agglutination. The results of some of these studies are presented in Table 1.

The Patients at the Time of Admission

An adequate study was carried out on the blood of 11 patients upon admission to the hospital (Table 2). The leukocyte count was high, usually 20,000 to 25,000 per cu. mm. but in one case it was 40,000 and in another 49,000. Both of these patients had multiple wounds of the legs. In both the evacuation time was long. The platelet count on admission was normal or high. The red cell count was usually about 4 million but the mean corpuscular volume was low and so was the hematocrit. The plasma hemoglobin was normal excepting a slight elevation in one patient who was receiving a transfusion of whole blood at the time of admission.

Table 2. Patients at Time of Admission

Patient	Wound	Evacuation Time (Hours)	Treatment en Route	Hct	MCV cu. μ	Plasma Hb mg./100 ml.	Leukocytes X 1000/cu. mm.	Platelets Million/cu. mm.	Transfusion (Pints of Blood)
K	Ext	5	0	46	71		23	0. 75	7
M	Chest	3	0	29	80	2. 5	17	1. 25	9
P	Abd	2	1 Gel	39	83	1. 6	24		6
Q	Ext	5	2 Dex 2 Bl	31	86	3. 8	25		6
R	Ext	2	0	50	90	0. 8	19		2
T	Ext	10	2 Alb	31	76	0. 5	40	0. 8	2
U	Abd	5	1 Dex	46	80		8	0. 26	4
V	Ext	2	1 Alb	35	82		27		3
EE	Ext	10	7 Bl	32	82	2. 6	49	0. 54	9
FF	Chest and Ext	4	1 Bl	32	79	11	22	0. 26	9
GG	Abd	2	1 Dex	37	80		23	0. 25	13

Abd=abdominal; Ext=extremity; Dex=500 cc. of .6 per cent Dextran; Bl=500 cc. of whole blood; Alb=200 cc. of 25 per cent serum albumin; Gel =500 cc. of 3 per cent modified gelatin; Hct=hematocrit; MCV=mean corpuscular volume. Evacuation time is the time elapsed between wounding and admission to the surgical hospital. The size of the transfusion is stated as an index of the severity of the wound.

Table 3. Leukocytes During Resuscitation and Surgery

Patient	Wound	Hourly Leukocyte Counts (X 1,000 per cu. mm.)							
		Preop.	1	2	3	4	5	6	7
1	Ext; abd	28	27	23	17	21	18	23	16
2	Abd	20	16	15	11	10			
3	Abd	4	3	13	8	6	6	3	11
4	Chest; ext	42	49	35	42	34	29	34	39
5	Chest; ext	33	27	26	21	19	15	16	
6	Ext; gangrene	19	26	32	13	12	10	14	10
7	Multiple ext	14	14	15	21	22			
8	Abd	12	7	11	11	7	9	13	
9	Pelvis; ext	25	13	15					
10	Femur	13	13	11	9				
11	Ext	22	19	18	17	13	14	14	
12	Abd	19	24	14	8	8	8	26	31
13	Buttocks; ext	19	11	8	9	10			
14	Abd; ext	20	35	43	32	24	21	14	
15	Abd; ext	5	5	5	5	6	6	3	2
16	Ext; back	36	69	39	26	29	33	24	20
17	Abd	29	24	11	7	5	5		
18	Ext	20	17	18	22	19	22	20	
19	Chest; abd	37	17	24	19	13	16		
20	Abd	27	37	29	23	26	24		

Abd=abdominal; ext=extremity. These patients are of a later series than those of the other tables.

The Patients After Operation

Leukocyte and platelet counts before and after operation are available on 17 patients of this series. In all but two the leukocyte count dropped. The average preoperative count was 24,000 per cu. mm.; postoperative 15,000. The platelet count usually rose although in two patients it fell. The average preoperative count was 450,000 per cu. mm.; postoperative 510,000. These averages do not include patients with hemoclastic reactions.[9] A second series of leukocyte counts was performed before and during operation at hourly intervals It demonstrated the various patterns of reaction to injury and transfusion (Table 3). In this second series patients 3, 12, 15, and 17 probably represent hemoclastic reactions characterized by an abrupt disappearance of leukocytes and platelets and a coincident fall of blood pressure. A most severe reaction of this sort was encountered in the patient presented below as case I. At the conclusion of operation his leukocyte count fell to 500 per cu. mm. and his platelet count to

17,000. Five hours later the leukocyte count was 2,700, the platelet count 375,000. At this time clotting time was 90 minutes in silicone, and clot retraction was poor. Eight hours after operation the leukocyte count was 3,510 and at 24 hours it was 11,150. Six different organisms were identified in a blood culture from this patient. In none of the patients with the hemoclastic reaction was fibrinolysis severe enough to cause bleeding.

A mild tendency to ooze from cut surfaces was noted in several patients who received transfusions of banked blood in excess of 20 pints. The bleeding phenomenon was little more than a source of annoyance to the surgeons who were able to control it easily by pressure. In these patients the clotting time, clot retraction, platelet count, and tourniquet test were normal. Prothrombin activity in these patients was studied.[20] It was found that the one-stage test of prothrombin time was much prolonged, indicating a defect amounting sometimes to a loss of more than 50 per cent of activity. Further tests indicated that the defect was on a basis of a relative lack of labile factor, one of the adjuvants of prothrombin conversion. It cannot be said that lack of labile factor underlay the mild tendency to bleed. The cause of this phenomenon has not yet been established.

Table 4. Reticulocyte Response to Anemia After Wounding

Patient	Blood Group	Replacement by Transfused Cells (% of Total RBC)	Age of Wound (Days)	Hematocrit	Reticulocytes (% of Total RBC)
M	A	60	11	36	1. 2
N	A	20	8	32	3. 6
P	A	50	8	26	5. 1
S	B	65	3	30	4. 4
V	A	25	5	27	3. 4
X	A	90	7	32	2. 0
FF	O	--------------	9	38	3. 2

Excepting FF there is a possibility that reticulocytes may have been destroyed as they appeared by foreign isoantibodies from the transfused group O plasma. The possibility becomes more remote each day after transfusion. In none of these patients was it possible to demonstrate such antibodies in vitro after the first day.

Reticulocyte counts were done on 15 patients. In eight, the reticulocytes were less than 1 per cent before and after operation. In six there were more than 1 per cent but in none more than 2 per cent. In one patient the reticulocytes percentage was 1.6 before operation and 0.6

afterward. Five to ten days after operation reticulocytosis had developed where anemia was present, but the number of reticulocytes was not appropriate to the degree of anemia (Table 4).

The plasma hemoglobin concentration was usually elevated immediately after operation (Table 5). The determination was carried out on 22 patients who had received from 2 to 37 pints of blood. In seven men (who had received 2 to 9 pints of blood) the plasma hemoglobin was normal. It was above 30 mg. per 100 ml. in five cases. The average postoperative hemoglobin level of all 22 patients was 18 mg. With three exceptions, the plasma hemoglobin concentration had returned to normal within 12 hours after operation. In these three, the postoperative level was 40 mg. or higher. In five patients, the plasma hemoglobin was measured frequently enough to establish the rate at which the pigment was cleared from the blood. In patients not in shock, the plasma hemoglobin decreased at rates that varied from 2.2 to 8 mg. per 100 ml. per hour. During severe shock, the rate of clearance was lower: 0.7 to 1.3 mg. per 100 ml. per hour. These results do not include the patients in whom the plasma hemoglobin concentration remained slightly elevated for several days, apparently as a consequence of continuing low-grade hemolysis (Table 6).

Table 5. The Effect of Large Transfusions on the Patients' Plasma Hemoglobin

Patient	Blood Group	Size of Transfusion (Pints)	Age of Blood (Days)	Average plasma Hb of Transfused Blood (mg./100 ml.)	Patient's Plasma Hemoglobin (mg./100 ml.)		Rate of Decline of Plasma Hb Postop. (mg./100 ml./hour)
					Preop.	Postop.	
B	A	20	11	26	47 (after 6 pts. preadmission)	31	5
AA	O	23	18–19	82	2	102	5
F	B	37	11 (26 pts.)	21	25		
			16 (11 pts.)	29	(after 14 pts.)	40	
G	A	8	17	31	12 (after 6 pts.)	8	
H	A	8	11	22	3 (after 4 pts. in 6 hrs.)	4	
I	A	13	13	NR		58	8 out of shock 0.7 in shock
K	A	7	12, 14	30		10	
BB	O	13	11–12	25		15	
M	A	9	10	19	2.5	18	
V	A	3	10	31		11	
P	A	6	11	19	1.6	3	
R	B	2	9	19	0.8	1.2	
DD	O	15	11	27	0.8	23 (after 11 pts. in 90)	4
Q	A	6	12	19	2.5	7.8′	
S	B	6	16	36	3.9 (after 4 pts. in 5 hrs.)	4.6	
EE	O	9	15–16	30	2.6 (after 7 pts. preadmission)	2.5	
FF	O	9	13	24	6 (after 4 pts.)	8	
GG	O	13	16	33		19	2.2
X	A	18	16–19	36		39	2.5
HH	O	0.8	31	132		28	1.5
Y	A	22	14–15	35		18	

Table 6. Effect of a Large Transfusion of Group O Blood in a Patient of Group AB

Date	Total RBC (Millions per cu. mm.)	Inagglutinable RBC (Millions per cu. mm.)	Proportion of Donated RBC (% of Total)	Plasma Hemoglobin (mg./100 ml.)	Titer of Anti-A Cold Agglutinin
Nov. 21 8 hrs. postop.	8.55	5.49	64	35	1:128 Direct Coombs test neg.
Nov. 22	7.81	5.26	67	19	
Nov. 23	6.68	5.42	81	21	1:128
Nov. 24	6.65	5.52	83	18	1:64
Nov. 25				14	
Nov. 26	6.68	5.71	85	5.2	1:64
Nov. 27	6.64	6.13	92	3.9	1:16
Nov. 29	6.81	5.74	84	2.3	1:8
Dec. 1	6.69	5.40	81		0
Dec. 4	7.10	5.41	76		0

Case D. Penetrating wound of the abdomen. 2000 cc. of mixed blood and intestinal contents were removed from peritoneal cavity. The patient was given 14 pints of group O blood in 7 hours, 10 of them within a period of 2.5 hours.

Note the increasing proportion of donor red cells indicating a progressive loss of native red cells. The plasma hemoglobin remained abnormal for several days, probably because of a mild intravascular hemolysis. The specific anti-A agglutinins may have been the mechanism whereby the native red cells were eliminated. Anti-B agglutinins were present in a titer of 1:2 at the time of operation but were gone within an hour postop. There were no nonspecific cold agglutinins until Dec. 1 when they appeared at a titer of 1:4 against group O red cells. The patient secreted B substance in his saliva but did not secrete A substance.

The mild hemolytic phenomenon was not apparent clinically. The patient's clinical course throughout this entire period was one of continual improvement.

Severe renal insufficiency developed in two patients of this series. One had an abdominal wound. His admission to our hospital had been delayed more than 24 hours. He received 4 pints of blood during his operation and was in moderate shock part of the time. Plasma hemoglobin after operation was 7 mg. per 100 ml. The other patient had an extremely severe wound of the pelvis and lower abdomen. He received 18 pints of blood. His plasma hemoglobin was 39 mg. at the time the last pint was being given. In neither of these men was it possible to relate the development of lower nephron nephrosis to the presence of hemoglobinemia of pathogenic concentration. The highest level of plasma hemoglobin encountered in any patient of this series was 102 mg. per 100 ml. in the patient AA. He did not develop renal insufficiency.

No cases of tetany developed on the basis of hypocalcemia from rapid transfusion of citrated blood. The single patient who had tetany did not respond to injections of calcium gluconate but improved when his hyperventilation was controlled.

All blood used for transfusion during this study was group O. The plasma of O blood contains antibodies against red cells of groups A and B. After transfusion, the blood of patients of groups A, B, and AB was examined to find if specific isoantibodies against A and B red cells had persisted. The results of this work are described in detail in another report.[8] In brief, it was found that the specific cold agglutinins against group A red cells persisted in the plasma of a few patients of groups A and AB. In most cases, the isoagglutinins were rapidly removed from the recipient's plasma even when he had been given enough blood virtually to replace his own plasma with donor plasma of group O. We found no case in which anti-B agglutinins persisted in the plasma of patients of group B or AB. The Coombs test for incomplete antibodies was also negative in all patients tested. Where the anti-A agglutinin persisted in high titer in the plasms of A or AB patients, there was definite evidence of specific hemolytic activity directed against the native red cells (Table 6). Where the replacement of native red cells by donor red cells was 80 to 90 per cent complete, the slow destruction of native cells continued, even in the absence of demonstrable group-specific antibodies. This hemolytic activity, which was demonstrated by laboratory methods was a low-grade process and had none of the clinical manifestations that are associated with incompatible hemolytic transfusion reactions.

In addition to this specific hemolytic activity there was evidence in severely wounded men of nonspecific hemolysis that destroyed native and transfused red cells indiscriminately. This loss of red cells was computed from blood volume determinations before and after transfusion which failed to account for all of the blood that had been administered.[24] It was also demonstrated by serial determinations of blood volume during the first two postoperative days. The loss was not due to hemorrhage. Postoperative bleeding was slight. In all probability, it was not due to sequestration. Some blood volume determinations demonstrated a delayed mixing of the tagged red cells, suggesting sequestration, but this only occurred when there was generalized congestion with a high hematocrit or when there was severe shock.[24] Patients B, S, and JJ are examples of the acute hemolytic phenomenon that occurred during the period or resuscitation. In many of the severely wounded there was evidence by cell survival studies of a moderate hemolytic activity during the period of 5 to 15 days after wounding (Table 1).

The more severely wounded men often tended to become anemic during the early days of their convalescence (Table 1). By measurements of red cell mass and plasma volume the falling red cell count and hematocrit were shown to be due to true anemia and not hemodilution.[24] Excepting in polycythemic patients an almost linear relationship was found to exist between the red mass and the hematocrit. In general, hemodilution occurred only to the extent that the plasma volume expanded to compensate for the loss of red cells.

Patients who tended to become polycythemic were those with abdominal wounds. In these patients the plasma volume was measured and found to be contracted. It is suspected that plasma is lost into the wounded bowel or into the abdomen. The total blood volume in the polycythemic patients was usually not abnormally great when measured by tagged red cells.[24]

The two patients who developed acute severe renal insufficiency became rapidly anemic at the time that they began to show clinical evidence of uremia. There had been slight or moderate hemolytic activity prior to this, as shown by changes in the Ashby counts, but with the onset of uremia the loss of red cells was precipitous. In one patient the hematocrit fell from 33 to 23 in 24 hours; in the other the red cell count fell from 5.24 million per cu. mm. to 4.65 million, a loss of 11 per cent in 24 hours. Neither patient had hemoglobinemia or bilirubinemia at the time. Other patients who developed renal insufficiency have been found to be icteric.[24]

Variations of Mean Corpuscular Volume

Variations of mean corpuscular volume (MCV) were found in all patients who were severely wounded. The MCV was uniformly low at the time of admission (Table 2). Immediately after transfusion the MCV was normal but usually within a day it again became abnormally low (Table 1). Thereafter it gradually returned toward normal. The changes in MCV were not accompanied by corresponding changes in the hemoglobin concentration of the whole blood. In blood smears and in the counting chamber there was no evidence of fragmentation of red cells to account for the reduction of MCV. The MCV of eight normal soldiers living in the same sector of the combat zone as the patients ranged from 86 to 96μ.[3] In six of the eight the MCV was 90.5 ± 1.0.

Discussion

The appearance of anemia during the days that followed resuscitation depended upon several factors. Red cells were lost in other ways than bleeding and the production of red cells was probably impaired. Except in a general way, it was not possible to define the degree of activity of each of the factors that caused anemia.

The Loss of Red Cells That Had Become Nonviable in the Stored Blood Used for Transfusion

During the refrigerated storage of blood preserved with ACD solution a progressively increasing number of red cells become incapable of survival in the circulation after transfusion. After 2 weeks of storage about 10 per cent of the red cells have become nonviable; at 3 weeks about 25 per cent are nonviable.[17] The Ashby technic has been widely used to study the post-transfusion survival of stored blood. Ashby counts were used in the present study but they showed little evidence of loss of transfused cells during the first 24 hours (Table 1). Indeed, in most cases the proportion of donor cells actually increased during that time though no more blood was transfused. In the interpretation of this observation certain points must be borne in mind. We must presuppose that the loss of nonviable red cells in these patients was at least as great as others have observed in normal recipients examined under better conditions. There are several important differences in the wounded patient:

1. The postoperative Ashby count was not a true reflection of the post-transfusion baseline. As much as 8 hours were consumed in the resuscitation and surgery of seriously wounded men. The nonviable red cells in the first blood given were undoubtedly gone when the postoperative sample was finally taken.
2. During surgery an indeterminate proportion of the donor red cells was lost through bleeding.
3. There was, as will be shown, a specific loss of native red cells when a large amount of group O plasma was transfused into a recipient of another blood group. The specific loss alters the proportion of native to donor red cells in favor of the donor cells, hence, the apparent increase of donor red cells in the first 24 hours after transfusion. An outstanding example of this reaction is shown in Table 6.
4. In some patients who received large transfusions and became polycythemic, an expansion of the circulating blood volume was demonstrated.[24] Changes in blood volume make the interpretation of Ashby counts difficult unless the magnitude of the change is known.

5. Severe wounds appear to be associated with nonspecific hemolytic activity against donor and recipient cells alike.

For these reasons, when a massive transfusion was given, it was not possible to compute the proportion of nonviable red cells by the Ashby method. With smaller transfusions these problems did not intrude. A single pint of blood should increase the inagglutinable count of an average-size man by about 0.5 million per cu. mm. The last six patients in Table 1 received small transfusions, and inagglutinable counts indicate little loss of red cells from nonviability during the first 24 hours after transfusion. The studies of plasma hemoglobin (Table 5) demonstrated little evidence of intravascular hemolysis which occurs if stored blood has deteriorated (patient AA). The loss of most nonviable red cells is believed to occur in the reticuloendothelial system without releasing pigment to the plasma.

From all of these data it seems justifiable to conclude that the post-transfusion destruction of red cells due to nonviability was not great. The loss of these red cells, even in association with massive transfusions, did not appear to impose a burden upon the excretory mechanism of the patients.

The Loss of Red Cells Due to Activity of Transfused Isoantibodies

When group O, universal donor blood is transfused into a recipient of another blood group, the plasma carries with it antibodies that are specifically active against the red cells of the recipient. The anti-A and anti-B antibodies consist of warm agglutinins, cold agglutinins, hemolysins, incomplete antibodies, and perhaps others which cannot be demonstrated excepting by their ability to eliminate red cells from the circulation.[17] The incompatibility of transfused group O plasma for the recipient's red cells is generally believed to be nonpathogenic excepting in the case of the dangerous universal donor. The dangerous donors have such a high titer of pathogenic antibodies that the blood produces acute hemolytic reactions when transfused into group A recipients.[15] No such reaction was observed in this series. During World War II Ebert and Emerson [13] demonstrated that mild hemolytic activity directed specifically against the recipient's A or B red cells was not uncommon after transfusions of universal donor blood or pooled plasma. Our own observations confirm this. It was noted above that the Ashby counts usually showed that the proportion of native cells decreased during the 24 hours after transfusion (Table 1). This is presumed to be the effect of transfused isoantibodies. In Table 6 is shown an outstanding example of this sort of reaction. In this patient it was possible to demonstrate a high titer of cold agglutinins specifically active against red cells of his own blood group. The foreign antibodies left his circulation slowly. It is important to note that the hemolytic activity of these antibodies did not produce any clinical reaction. During the time he was under observation the patient progressively improved. His convalescence was no less rapid than that of others with similar wounds in whom no such hemolysis occurred, they being of group O. However, there is in this situation a matter of great clinical importance. There existed a potential danger to patients who had been given 18 or 20 pints of group O blood, thus virtually replacing their own red cells and plasma by donor cells and plasma.

After several hours or days it often became necessary to give additional blood to such a patient. Fresh blood was available from troops in the neighborhood and there was a temptation to ask for group-specific blood rather than to continue with group O, universal donor blood. The problems of type and cross match were formidable. Ninety-five per cent or more of the red cells in such a patient's circulation may have been replaced by group O. The identification of his own group on the basis of the agglutination of less than 5 per cent of the red cells involved more judgment than one should expect of most technicians. If foreign isoagglutinins persisted in the patient's plasma, as they did in the patient shown in Table 6, it was impossible to match his blood with donor blood of his hereditary group. It was possible, of course, to obtain a satisfactory cross match if blood were drawn from the patient before the beginning of the transfusion of O blood. It was also possible to give group-specific blood without cross matching. We believe that both of these procedures are dangerous and may lead to several reactions. No such reaction occurred during this study, but in the records of several of the hospitals in Korea we found circumstantial evidence to indicate that such reactions had actually occurred. See the abstract of Case KK. See also page 72. When a man has been given a large amount of universal donor blood, it is recommended that he continue to receive universal donor blood should he need subsequent transfusions during a period of 2 weeks. After this time it seems fairly certain that the foreign isoantibodies will be gone from his circulation.

The Loss of Red Cells Associated With Damage or Destruction of Large Amounts of Tissue

The members of the Surgical Research Team had evolved a rule of thumb: "Abdominal cases become polycythemic; amputees become anemic." The rule was a good one, and its applicability was especially obvious in the severely wounded of each category.

The most obvious difference between the two types of wound was the amount of tissue that was damaged or destroyed. A severe abdominal case may have been wounded by a single small-arms missile that perforated the stomach and colon to cause massive contamination of the peritoneum, often with little loss of blood. This patient would develop a refractory type of shock and was then given 8 to 12 pints of blood, in the expectation that the red cells would fill the relaxed and sluggish parts of his circulation. When his blood pressure recovered, the patient sometimes became plethoric and congested, and sometimes showed signs of incipient pulmonary edema. His hematocrit would lie between 55 and 65. During the period of convalescence when he was under our observation, the hematocrit might recede slowly (case A, Table 1; case D, Table 6; abstract of case AA). The patient who stepped on a land mine and suffered a bilateral high thigh amputation reacted quite differently. With competent tourniquets in place he might be given 12 transfusions in 2 hours and not develop congestion nor a high hematocrit. He might even require more blood to complete his operation and he might need another transfusion the next day or so because of anemia. (Abstracts of cases B, S and JJ are examples of this.) The fate of this transfused blood has not been proved. Certainly it was not all lost by bleeding. Some of it may have been extravasated into wounded tissues. Sequestration was a possibility but not a likely one: these patients may not ever have been in shock, or if they were their blood pressures soon recovered; blood volume studies did not show evidence of sequestration that was sometimes encountered in the plethoric abdominal case and which revealed itself as delayed mixing of injected tagged red cells.[24] We are left with the possibility of hemolysis which includes the destruction of extravasated blood. This appears to be a fairly good possibility.

During World War II several investigators [14, 23] commented upon the tendency of patients with traumatic amputations to become markedly oligemic (a term that implies a reduction of the mass of circulating red cells). Cleghorn *et al.*,[5] on the basis of computations of circulating blood volume and size of transfusions given, came to the conclusion that hemolysis must contribute to the loss of red cells. On the basis of similar computations, we have arrived at the same conclusion. Furthermore, it seemed probable that this particular hemolytic process rapidly subsided but did not always disappear. In some patients it persisted well into the period of convalescence. (For examples, see case P, Table 1, or the abstract of case B. Compare them with the abdominal cases, A and H in Table 1.) When the loss of red cells slowed down, the evidence of persistent hemolysis was apparent in the rapidly declining proportion of donor red cells. This decline has nothing to do with nonviability. The normal rate of replacement of donor red cells is less than 1 per cent a day (patient H). In patient G the donor cell count fell at a rate of 2.5 per cent per day but replacement was adequate and no anemia developed. In patient P it fell at 5 per cent per day, replacement was not adequate, and anemia appeared. In patient S (case abstracts) the loss was at least 12 per cent per day. Several of the patients of this series were evacuated to Walter Reed Army Hospital where the Ashby counts were continued. These counts indicated that after the first few weeks of convalescence the survival of red cells transfused at the time of wounding became normal.

The clinical significance of the distinction between the abdominal wound and the traumatic amputation was thoroughly known to the surgeons who cared for these men. It was important not to push transfusion too vigorously in the patient with an abdominal wound who was not bleeding. It was of equal importance to use blood rapidly and in large amounts in a patient with a bilateral amputation. Such a patient might develop severe anemia while a slow transfusion was actually being administered. The U. S. Army's Field Research Team in Italy during World War II observed a patient with bilateral traumatic amputation of the thighs, a wound similar to that of our patient, JJ. It was reported that it was not possible to transfuse the patient in Italy rapidly enough to save his life.[2] The use of air pressure to speed the injection of blood and the use of arterial transfusions may well be lifesaving in such cases. It is recommended that the hemoglobin of these patients be determined accurately, rapidly, and repeatedly during resuscitation and for at least 48 hours thereafter.

The Loss of Red Cells Associated with Acute Renal Insufficiency

Acute nephritis is known to cause anemia. The anemia has been shown to be a result of two factors: abnormal hemolysis and impeded erythropoiesis.[16, 18] The severely wounded who develop acute post-traumatic renal insufficiency (lower nephron nephrosis) usually become anemic rapidly, as revealed by a falling hematocrit and a shrinking of red cell volume.[24] The hematocrit may fall 10 points in 24 hours. This may happen 10 days after wounding when the hemolysis associated therewith has greatly diminished. The loss of red cells in the uremic patient was not accompanied by hemoglobinemia or marked bilirubinemia. The reticulocyte count was somewhat increased in these patients before the onset of uremia, but it fell below 1 per cent even though anemia increased at the same time. This may have been an indication of impairment of red cell production.

The Inadequacy of the Bone Marrow's Response to Anemia

It is pointed out above that many of the severely wounded were prone to develop anemia, and that hemolysis is probably a factor in the pathogenesis of the anemia. During the first week or 10 days of convalescence a severely wounded man may destroy his red cells at three to five times the normal rate. Evidence has been published to suggest that the adult human bone marrow can produce hemoglobin at six to eight times the normal rate; blood destruction can therefore take place at six to eight times the normal rate without appearance of anemia.[7] The bone marrow of the seriously wounded men did not compensate to this extent. When they destroyed their red cells at only four times the normal rate, they became anemic. Reticulocyte counts also showed evidence of impaired response to anemia (Table 4). With an hematocrit of 25 one would expect a reticulocyte count of 15 to 20 per cent instead of 5 per cent.

Pigment Metabolism

If the 300 mg. of hemoglobin from 1 ml. of red cells were released at one time into the plasma of an average-size man (plasma volume 3,000 ml.), it would raise the plasma hemoglobin 10 mg. per 100 ml. If instead of being released into the plasma the same amount of hemoglobin were degraded to bilirubin in the reticuloendothelial system and if all of the bilirubin appeared in the plasma at the same time, it would raise the plasma bilirubin 0.35 mg. per 100 ml.

In the face of a hemolytic process that appeared to involve hundreds of ml. of red cells, as with such patients as B and JJ, it is remarkable that there was little evidence of pigment liberation. The route of its removal remains obscure. Hemoglobinuria did not appear in any patient of this series. Indeed, the level of plasma hemoglobin did not approach the renal threshold (130 mg. per 100 ml.) except in a single case (AA). The slight or moderate elevations of plasma hemoglobin almost invariably subsided to normal within 12 hours. The return to normal was slow in patients with evidence of intravascular hemolysis due to poor quality of transfused blood (AA) or due to destruction of native red cells by transfused isoantibodies (Table 6).

In most of the patients with severe wounds the plasma bilirubin showed a slight or moderate biphasic elevation that was shadowed by a similar increase of urinary urobilinogen excretion.[21] Patient AA was the only one of this series whose plasma bilirubin exceeded 4 mg. per 100 ml. Patient B was a typical case. Patient JJ with no elevation of plasma bilirubin was exceptional. It has been noted by the Surgical Research Team that patients with paralytic ileus almost always became jaundiced. The reason for this has not been established. Clinical jaundice was rarely encountered in other patients. The rate of excretion of bile pigment in the feces could not be studied because the severely wounded rarely defecate during the first week or 10 days.

The Leukocytes and Platelets

Leukocytes and platelets of blood preserved in ACD solution are nonviable.[17] Although they may be visible in the stored blood they disappear immediately from the circulation of the recipient. The transfusions given to some patients of this series were large enough virtually to replace their own blood with blood that was, in effect, free of leukocytes and platelets. The leukocyte count was not seriously depressed by large transfusions (Table 3). The production of new leukocytes was adequate to prevent leukopenia. The platelet level was generally unaffected by dilution or replacement of the patient's blood by large transfusions.[20] In fact, the platelet counts usually increased. The production of platelets was adequate and the platelets themselves seemed competent as judged by bleeding time and clot retraction.

These results are somewhat at variance with other observations of the effect of transfusion on leukocyte and platelet levels. Stefanini and Chetterjea [22] have reported a slight drop of leukocytes and a marked fall of platelets following the transfusion of small amounts of compatible plasma, even in normal subjects. Desforges [12] has found that exchange transfusion causes a profound fall of platelets in infants treated for hemolytic disease of the newborn and patients given massive transfusions because of gastrointestinal hemorrhage. It is pointed out that the patients in the present series were conditioned by severe injuries incurred several hours before transfusion which evoked leukocytosis and thrombocytosis. This conditioning may have enabled the patients to withstand the large transfusions without developing a lack of leukocytes or platelets.

Changes in the Mean Corpuscular Volume of the Red Cells

The severely wounded showed consistent changes in the mean corpuscular volume of the red cells. The MCV was abnormally small on admission, tended to become normal again during resuscitation and became small again thereafter (Tables 1 and 2). There was no evidence of fragmentation of red cells and the hemoglobin concentration of the whole blood did not change. This indicates that as the cell volume decreased the hemoglobin concentration in the individual cells increased. The changes in volume thus were due to shifts of water which may in turn have been related to shifts of electrolytes. The problem is being studied further. Thorn and his collaborators [27] have described similar changes in red cell hemoglobin concentration following the administration of ACTH and cortisone. The changes of MCV in the severely wounded may reflect a stimulation of the adrenal cortex. Because the change in MCV was sometimes as great as 15 per cent it is suggested that this variable should be taken into account in blood volume studies which involve shock or trauma.

The Hemoclastic Reaction

On several occasions there occurred an abrupt and profound fall of leukocytes and platelets associated with a sudden drop in blood pressure. During the subsequent several hours the counts gradually recovered (Table 3). This was interpreted to have been a manifestation of a hemoclastic reaction, a reaction that involves, in addition to an abrupt disappearance of white cells and platelets, many changes in the globulin enzyme systems of the plasma.[9] The hemoclastic reaction occurs in response to many types of injurious agents: foreign protein, peptone, incompatible blood transfusion, etc. We observed the reaction in men who had severe abdominal wounds with gross soiling of the peritoneum. It was suspected that the reaction may have been due to contamination of the blood stream via the lymphatics of the diaphragm. During the hemoclastic reaction in one man a blood culture revealed the presence of six different organisms.

Effects of Massive Transfusions

Evidence of the deleterious effects of massive transfusions did not materialize in the course of our investigation. Pulmonary congestion appeared in several patients who were given large rapid transfusions, but full-blown left-sided heart failure was not encountered. It is significant that these patients were healthy before they were wounded, and they were 20 years of age. Fibrinolysis did not occur as a clinical hemorrhagic state nor could it be demonstrated in incubated clots. This is at variance with civilian experience with massive transfusions during operations for widespread cancer; mild degrees of fibrinolysis are commonplace and severe hemorrhagic reactions have occurred from time to time.[*, 25]

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*Subsequent to this study it is probable that several fibrinolytic reactions were encountered in the forward surgical hospitals in Korea. They occurred in the course of massive transfusions and were characterized by excessive bleeding and by apparent incoagulability of shed blood in vitro. There were no fatalities among the patients of whom we have knowledge. The rate of fibrinolytic reac-

The plasma hemoglobin of the bank blood was not unduly high, an indication that the blood had been well preserved during shipment. The levels of free hemoglobin would have been much higher if refrigeration had not been adequate. Following large transfusions of stored blood the plasma hemoglobin of the recipients was not especially high. It was usually of the same order as that of the plasma of the bank blood given them (Table 5), and that hemoglobin rapidly disappeared. Even though 10 to 20 per cent of the red cells may have been nonviable their hemoglobin was not released into the blood stream where it would impose an excretory burden on the kidneys. Among the casualties in Korea it has not been possible to relate the incidence of post-traumatic renal insufficiency with hemoglobinemia. It had been shown [19] that the combination of prolonged deep shock and the infusion of methemoglobin solutions in dogs can produce a renal tubular lesion similar to that of post-traumatic renal insufficiency (lower nephron nephrosis). The concentration of plasma hemochromagen that occurred in these dogs was 800 to 2,000 mg. per 100 ml. This severe hemoglobinemia caused no demonstrable lesion if hypotension was inadequate or brief.

The post-transfusion hemoglobinemia encountered in Korea has not approached these concentrations except where an obvious incompatible transfusion reaction occurred, and these have been rare. The Renal Treatment Center of the U. S. Army receives all patients of the United Nations Forces who develop renal insufficiency. In 1952 only four patients were transferred to that Center with evidence of post-transfusion hemoglobinuria.[26] Over 60,000 transfusions were given in Korea in 1952. This helps to place in proper perspective the role of free hemoglobin in the pathogenesis of post-traumatic renal insufficiency.

The use of universal donor blood in the combat zone is a valuable military expedient. Because only one blood group is involved, an adequate reserve can be maintained with fewer units of blood. Small but effective banks of blood can be established at the forward aid stations. By eliminating the need for a cross match, transfusion can be started as soon as a patient is admitted. It also eliminates the incompatible transfusion reactions that inevitably occur where group-specific blood is used. That only four cases of post-transfusion hemoglobinuria were admitted to the Renal Treatment Center in 1952 indicates that incompatible transfusion reactions are rare under this system. It is of interest that each of these four cases resulted from

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tions based on this information is estimated to have been less than 1 per cent among patients who received more than 10 pints of blood. (Personal communications from Major C. P. Artz, MC, U. S. Army, and Commander R. N. Grant, MC, U. S. Navy.)

the use of group-specific blood that was locally procured.[26] In two cases there apparently was a mistake in typing or cross matching. The other two were similar to patient KK whose case is abstracted below. Field conditions being what they are, it is not surprising that occasional errors have occurred. It was fortunate that there was little need for local procurement of blood. The blood that was sent to Korea was obviously correctly typed and the dangerous universal donors were adequately identified.[1]

Summary

1. During the third winter campaign in Korea, the hematologic reaction to wounding was studied in 37 casualties at the time of initial resuscitation.

2. Of particular interest was the effect of massive transfusions of stored blood. The results of storage of blood—high plasma hemoglobin and potassium, low labile factor activity, nonviable platelets and leukocytes—had little deleterious effect on patients who received as much as 20 to 30 pints in less than 6 hours. The loss of transfused red cells because of nonviability was no more than expected.

3. At the time of resuscitation and shortly thereafter, there was a remarkable loss of circulating red cell mass in patients with wounds that involved much tissue destruction. It is believed that the loss was due to hemolysis but the mechanism is unknown. The loss of red cells may be so rapid that a patient with bilateral traumatic amputation of the legs and an adequate hemostasis would become severely anemic if one hesitated to use large, rapid transfusions. Patients with severe shock whose wounds involved less tissue damage (lacerated colon, for example) did not destroy red cells in this fashion. After moderate transfusions, such patients often became polycythemic. Transfusions had to be carried out rather gingerly because of a tendency to develop signs of congestion.

4. During the early days of recuperation from severe wounds the patients often tended to become anemic. The anemia appeared to be the result of hemolytic processes plus a relative inhibition of red cell formation.

5. Universal donor blood, group O, was used in all transfusions. In patients who are not group O the massive transfusions resulted in the virtual replacement by red cells of another group. The patient's plasma sometimes contained antibodies against red cells of his hereditary blood group. Gradual hemolysis of native red cells by transfused antibodies was observed. This was not a clinical hemolytic reaction and did not appear to be detrimental to the patient. The presence of the foreign antibodies made it impossible in some cases to cross

match the patient with blood of his hereditary group and suggested a source of danger in attempting such transfusions. After transfusion with the universal donor blood has begun, it is recommended that no change be made to blood of another group until at least 2 weeks have elapsed.

6. No incompatible transfusion reactions were encountered. Several hemoclastic reactions may have been caused by gross contamination of the blood stream from the site of wounds or from the peritoneal cavity.

Abstracts of Representative Cases*

Case A: Age 20, weight 145, blood group A, was wounded in action 5:00 p. m., November 13, with multiple penetrating wounds of the abdomen. He was admitted to the hospital at 9:00 p. m. in a condition of moderate shock. He was found to have multiple lacerations of the descending colon and was bleeding from the mesentery. The left femoral and brachial arteries were perforated. Both were repaired. During resuscitation and surgery the patient was given 9 pints of whole blood. At the conclusion of surgery, his hematocrit was 55. Ten days later without having been given any further transfusion, the hematocrit was 44. Throughout this period the proportion of group O red cells in the circulation remained 65 per cent.

Case AA: Age 22, weight 165, blood group O, was seriously wounded in action 9:30 a. m., November 17, by a mortar fragment which penetrated the left side of his chest, left lung, diaphragm, stomach, spleen, pancreas, left kidney, and lodged in the psoas muscle. He was in shock on admission to the hospital, was resuscitated and again went into shock during surgery. During this time he was given 23 pints of blood. His left kidney was removed. Twenty-one of the 23 pints of blood were 18 or 19 days old, 5 pints had a plasma hemoglobin of 100 ml. or more. The average plasma hemoglobin of the 23 pints was 82 mg. per 100 ml. which was more than double the average of all of the pints of blood examined during this study. These bottles were all of the same lot, which suggested that a break in refrigeration had occurred. Immediately after operation (9:00 p. m.) the patient's plasma hemoglobin was 102 mg. per 100 ml., plasma bilirubin 2.1 mg. The next morning the plasma hemoglobin was 24 mg. per 100 ml., the plasma bilirubin 8.1 mg., 3.8 mg. of which was indirect. The patient never became oliguric. His NPN on the third postoperative day was 67 mg. per 100 ml. The patient's hematocrit receded slowly. It was 60 on the first postoperative day. Fifteen days later it was 48.

Case B: Age 19, weight 140, blood group A, was seriously wounded in action 5:00 p. m., November 15, when he stepped on a land mine. The injury necessitated high amputation of both thighs. He was admitted to the hospital at 9:00 p. m. having received 6 pints of blood en route. The tourniquets on his thighs were competent. Donor red cells represented 63 per cent of the total in his circulation. The hematocrit was 40, total blood volume (Ashby) 4,000 ml., plasma hemoglobin 34 mg. per 100 ml., plasma bilirubin 0.4 mg. per 100 ml. He was given 6 more pints of blood before operation. During surgery he was given 8 more pints of blood. His blood loss did not exceed 1,500 ml. After surgery the donor red cells were 87 per cent of the total. The hematocrit was 39;

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*Details may be found in the tables.

plasma hemoglobin 31 mg; plasma bilirubin 2.3 mg. Six hours later the donor red cells were 98 per cent of the total.

He had been given no transfusion meanwhile. Presumably many of his native red cells had been eliminated by the activity of anti-A antibodies in the transfused plasma. At this time his plasma hemoglobin was 2 mg., plasma bilirubin 2.6 mg., hematocrit 36. The blood volume was 3,500 ml. (Evans' Blue). The patient was not in shock any time after transfusion was started at the battalion aid station. Following operation the volume of red cells to be accounted for was as follows: 1,500 ml. in his circulation at the time of admission plus 2,600 cc. in the 14 pints of blood transfused thereafter. It was possible to account for 1,300 ml. of red cells which were in the patient's circulation after operation, plus 1,000 ml. which had been lost during operation and by specific hemolysis of native red cells. The discrepancy amounts to 1,800 ml. of red cells, which is the equivalent of about 10 pints of bank blood.

Case DD: Age 19, weight 160, blood group O, was accidently wounded in the shoulder with a small-arms missile at 3:00 p. m., December 17. He was evacuated to the hospital by helicopter arriving at 4:30 p. m. He had a massive hemothorax of the left side of the chest. He was given 4 pints of blood before operation and taken to the operating room at 6:30 p. m. When his chest was opened there was a sudden severe hemorrhage from a laceration of his left subclavian vein. Between 7:00 and 8:00 p. m. he was given 11 pints of blood. At the conclusion of this rapid transfusion, his plasma potassium concentration was 4.65 mEq. per liter. His plasma hemoglobin was 23 mg. per 100 ml. His white cell count was 20,000 per cu. mm. At 11:00 p. m., the plasma potassium was 4.17 mEq. and the plasma hemoglobin 11.5 mg. The plasma hemoglobin of the transfused blood averaged 23 mg. per 100 ml. The blood was 11 to 14 days old. The next morning the patient's hematocrit was 47. His red cell volume (radiochromium) was 1,550 ml.

Case I: Age 20, weight 170, blood group A, was seriously wounded in action, 9:00 p. m., December 1, by a shell fragment that penetrated the transverse colon and proximal jejunum. He was admitted to the hospital at 3:00 a. m. the next morning. He was given 4 pints of blood preparatory to operation. He went to the operating room at 6:00 a. m., was given 8 more pints of blood by 8:00 a. m. His blood pressure fell throughout surgery. Two liters of mixed blood and intestinal contents were removed from his abdomen. Otherwise blood loss was slight. At the conclusion of surgery the patient had signs of pulmonary congestion and appeared plethoric. His hematocrit at this time was 59. During the next hour the hematocrit rose to 64; blood volume determination (red cells tagged with radioactive chromium) showed the red cell volume to be 7,600 ml. Therefore, the total blood volume was approximately 10,200 ml. This patient had a severe hemoclastic reaction at the conclusion of surgery. He died 30 hours after operation.

Case JJ: Age 21, weight 170, blood group O, was severely injured while hunting when he stepped on a land mine, causing a high bilateral traumatic amputation of his thighs. The accident was witnessed by two medical soldiers from our hospital who applied tourniquets, stopped an ambulance and brought him to the hospital about 45 minutes after the accident occurred. He was exsanguinated, pulseless; respiratory rate 8 per minute. Intravenous transfusions were commenced on both arms and the injection of blood was speeded by pumping air into the bottles. A surgeon cut down on the stump of the left femoral artery and when a cannula had been inserted a rapid intra-arterial transfusion was begun. Within 30 minutes he had received almost 20 pints of blood. He recovered consciousness and blood pressure, but developed transient pulmonary edema. The transfusion was slowed.

On the way to the operating room the tourniquets became dislodged and before they could be reapplied he lost 2 liters of blood. The transfusion was continued. Upon induction of anesthesia the patient again fell into shock. The anesthetic was stopped, and the patient again recovered. He was then returned to the ward without surgery. The tourniquets had remained competent and subsequent blood loss was negligible. The period of resuscitation had occupied 5 hours during which the patient received 32 pints of bank blood. At the time of his return to the ward the hematocrit was 39. The next morning it was 38, and he was given 4 pints of fresh, locally procured blood. At this time the plasma hemoglobin was 2 mg. per 100 ml. and the plasma bilirubin was 0.7 mg. A day later the hematocrit was 28, and there had been no bleeding except for some oozing from the stumps of his thighs. He was given 6 more pints of fresh blood and the stumps were amputated. The patient recovered. He did not become oliguric.

Case KK: Age 19, blood group B, was seriously wounded in action 9:00 p. m., July 22, by an enemy mine. There were severe wounds of the head, abdomen, both legs, and left arm. He was admitted to the hospital at 5:30 a. m. having received 2 pints of blood en route. He was given 4 more pints and taken to the operating room at 8:00 where laparotomy, craniotomy, and débridement of the extremities were carried out. When he left the operating room at 12:00 noon he had received a total of 17 pints of group O blood 13 to 15 days old. His plasma hemoglobin was 55 mg. per 100 ml.; plasma potassium was 5.8 mEq. per liter; hematocrit 43. That evening because of unsteady blood pressure the transfusion was resumed. The patient was given 6 pints of fresh group B blood. During this transfusion the patient's blood pressure fell even further. His plasma was found to be dark red and contained 990 mg. of hemoglobin per 100 ml. The plasma potassium at this time was 6.4 mEq. per liter. During the night the patient's blood pressure was maintained above 100 mm. Hg by norepinephrine, but it fell the next morning and the patient died at noon. After his operation he produced 485 ml. of urine but none after hemoglobinemia appeared.

This patient was not one of our series. The information was obtained from hospital records.

Case S: Age 22, weight 135, blood group B, was wounded in action 1:30 a. m., December 22, with multiple wounds of both legs, necessitating mid-thigh amputation of the left leg. He was given 3 pints of blood at the battalion aid station and en route. He arrived at the hospital at 7:00 a. m. He was never in shock. On the basis of Ashby counts performed before operation it was estimated that 50 per cent of his blood had been replaced and that his blood volume was approximately normal. Hematocrit was 46. He had lost by bleeding and hemolysis perhaps 1,000 ml. of his own red cells. Loss during surgery was less than 400 ml. of red cells. During evacuation and surgery he was given a total of 6 pints of whole blood, which is the equivalent of about 1,100 ml. of red cells. (The hematocrit of bank blood is about 37.) We assume that the patient had 2,000 ml. of red cells before he was wounded. He received by transfusion 1,100 ml. of which 20 per cent, at the outside, were lost by reason of nonviability. Therefore, 2,900 ml. must be accounted for. Before the operation 1,000 ml. had been lost; during the operation 400 ml. were lost; 2,900 ml. less 1,400 ml. would leave 1,500 ml. to be accounted for in his circulation after operation. On December 24, his red cell volume (radiochromium) was 700 ml., a discrepancy of 800 ml. The plasma volume (Evans Blue) was 2,460 ml. Hematocrit was 30. The decline in the Ashby count between December 23 and 24 indicated that the transfused cells were being replaced at a rate of 12 per cent per day, at a time when most or all nonviable red cells would have been removed. Such a change in the Ashby count is characteristic of hemolytic disease where the bone marrow produces red cells for replacement. The patient's reticulocyte count on December 24 was 4.4 per cent.

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Chapter 7

Some Immunohematologic Results of Large Transfusions of Group O Blood in Recipients of Other Blood Groups*

A Study of Battle Casualties in Korea

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Because group O red cells contain no A or B antigens they may be transfused into anyone without precipitating a reaction in the ABO blood group system (excepting, of course, the very rare persons with anti-O or anti-H). Although the group O cells are innocuous the use of so-called universal donor blood in patients of groups, A, B, or AB involves an incompatibility "on the minor side," since the plasma of the donor contains antibodies against the red cells of the recipient. Occasionally a dangerous universal donor is encountered whose plasma contains antibodies of a nature and of such high titer that transfusion into A or AB patients may cause a severe hemolytic reaction.[9, 10] With low-titer group O blood, it is possible that the plasma of the recipient dilutes and neutralizes the foreign antibodies and prevents hemolysis.

Most of the knowledge of universal donor transfusions is based upon experience involving 1 or 2 pints of blood. What occurs when larger quantities of blood are used? If, for example, 20 pints of O blood were given to a subject of Group A, B, or AB, would the accumulation of isoantibodies finally become pathogenic and destroy the recipient's native red cells? Would the patient's blood become temporarily altered to group O? If it were, would the transfusion of blood of the patient's hereditary group produce an incompatible reaction? An opportunity was recently afforded to study the effects of such transfusions in Korea. Only group O Rh-positive blood was shipped to the combat zone in Korea and this blood was given without preliminary cross matching to all casualties irrespective of their blood group. Enormous transfusions were sometimes used. In severely wounded men 10 or 20 or even 30 pints of blood might be given within a few hours. All of the blood transfused had been previously screened for the presence of high-titer isoagglutinins to identify the dangerous universal donors. For this purpose, the screen appears to have been

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adequate. Thus, in the year 1952 over 60,000 transfusions were given in Korea, and during this period only four patients were admitted to the Renal Insufficiency Center with a history of post-transfusion hemoglobinuria. Each of the four had been given blood that was procured locally in Korea.

The present study was undertaken to learn if less severe reactions occur on the basis of incompatibility on the minor side, and to learn if such reactions contribute anything to the development of acute renal failure in the severely wounded.

Materials and Methods

1. General Conditions

The study was carried out in the laboratory of the Surgical Research Team of the U. S. Army in Korea during the winter of 1952–1953. The laboratory was attached to the 46th Army Surgical Hospital. The patients were young soldiers who were received by ambulance or helicopter usually within 1 to 3 hours after they had been wounded. Transfusions of whole blood or plasma substitutes had often been begun at aid stations before the patients reached the hospital. Transfusions were continued as needed throughout the period of resuscitation and surgery. In some patients as much as 37 pints of blood were used within a period of 12 hours. As much as 20 pints have been given within 1 hour. The blood shipped to Korea was collected in the United States or from United States troops in Japan.

The blood was 8 to 10 days old when it was received at the hospital. Most of it was used before it was 15 days old. It was discarded if it had not been used when it was 21 days old.

2. High-Titer Screening

All of the blood was group O, Rh positive and was used without cross matching, irrespective of the blood group of the recipient. Each bottle of blood had been tested for high-titer isoagglutinins active against group A and B red cells. The serum was diluted 1:200 (Tokyo) or 1:256 (California). Equal volumes of a 2 per cent suspension of red cells and the diluted serum were mixed, and readings were made after incubating 10 minutes at room temperature. In California, the test was read on a tile; in Tokyo it was read in test tubes. Where agglutination occurred the blood was called high titer and was intended to be given to group O recipients. Where there was no agglutination the blood was considered to be low titer and could be given to anybody. In California 45 per cent of the O blood was high titer, but only 15 per cent of that flown to Japan was high titer. In Tokyo 35 per cent of the blood collected was high titer.

3. Hematologic Methods

The technical work of the present study was performed by one of us (WHC). Red cell counts were done by the method of Dacie [7] in which 20 cu. mm. of whole blood were diluted in 5 ml. of normal saline (1:250). The same 5 ml. and 20 cu. mm. pipets were used for every determination. After thorough mixing, the cells were counted in a standard hemacytometer. Differential agglutination (the Ashby technic [12]) in A, B, and AB recipients was carried out by pipeting 0.3 ml. of the 1:250 red cell suspension into a small test tube that contained an estimated 5 mg. of dried anti-A or anti-B typing serum (Michael Reese). This caused agglutination of the patient's native red cells but did not agglutinate the transfused group O cells. After 30 minutes the tube was centrifuged at 400 rpm for 1 minute and the unagglutinated red cells were resuspended and counted in a hemacytometer. Baseline inagglutinable counts were not always obtained because transfusion was often begun before arrival of the patient at the hospital. When baselines were done, the count varied between 7,000 and 15,000 per cu. mm. In making the total red cell counts and Ashby counts at least 1,500 cells were counted; where the two values were almost equal, at least 3,000 cells were counted. The Ashby counts were of value to establish the ratio of donor (group O) red cells to native (A, B, or AB) red cells after transfusion. Serial Ashby counts revealed alternations of the ratio. An increase in the proportion of agglutinable native red cells suggested a loss of transfused cells. An increase of inagglutinable group O red cells suggested a loss of native cells. Under normal conditions transfused cells are replaced by newly generated native cells at the rate of 0.85 per cent per day.[12] Reticulocyte counts were done by the method of Brecher [3] using new methylene blue; normal counts were 0.4 to 1.0 per cent of total red cells. Plasma hemoglobin was performed by a method described elsewhere,[5] modified by using benzidine rather than benzidine dihydrochloride as the indicator. This was in an aqueous solution rather than alcoholic, and the values obtained are probably about 30 per cent low.[4] The normal plasma hemoglobin was less than 5 mg. per 100 ml.[5]

4. Immunologic Methods

The tests for antibodies were performed on serum or lightly heparinized plasma. There was no difference in results when serum and plasma were obtained and tested simultaneously. The blood was placed in a tube and allowed to clot or sediment at 37 C. for 2 hours. There was no evidence of hemolysis in vitro in these tubes. The plasma was centrifuged and a quantitative test for plasma hemoglobin was done. In testing for agglutinins the serum or plasma was doubly diluted with saline and an equal volume of a 2 per cent suspension of red cells was added. When two or more types of red cells were used the suspensions were matched to assure the same concentration of cells. A_1 cells were always obtained from the same source; no study was made with A_2 red cells; B cells were obtained from two sources; O cells were obtained from numerous sources including stored blood.

The serum-cell suspensions were refrigerated for 2 hours at 3 to 5° C. The tubes were then centrifuged at 400 rpm for 1 minute, returned to the ice bath for 5 minutes after which they were shaken and read. Agglutination was rated from trace to 4 plus. A trace was the least agglutination that could be detected grossly when compared with an unagglutinated control. At 4 plus all cells were clumped in one or two large masses. After refrigeration the tubes were placed in warm water for 20 minutes and the process of centrifugation and reading was repeated. At 37° C. the first tube was examined for evidence of hemolysis. There was none but the addition of the small amount of typing serum that contained isohemolysin would cause the cells to lyse, indicating adequate complement activity. Agglutination of group O cells was interpreted to be due to nonspecific cold agglutinins. Agglutination of A and B cells was compared with that of O cells. If it was no greater, it was called nonspecific. Where anti-A or anti-B titer exceeded the nonspecific agglutination it was regarded as due to a specific isoagglutinin. The titer was taken as the difference between the specific and the nonspecific agglutination. The blood of patients whose plasma contains isoagglutinins was matched against 15 to 20 bloods each of groups A_1 and O to confirm the specificity of the agglutinin against A. The direct Coombs test was performed according to the directions of Dacie,[7] using an anti-human-globulin rabbit serum prepared at the Immunology Division, Army Medical Service Graduate School.

Saliva was tested for the presence of A or B substance as follows: The saliva in a test tube was placed in boiling water for 20 minutes. It was then centrifuged and the clear supernatant material was diluted with saline 1:4 and 1:8. Higher dilutions were sometimes made. One-tenth ml. of this material was added to 0.1 ml. of anti-A or anti-B typing serum and allowed to stand at room temperature for 30 minutes. Then 0.1 ml. of a 2 per cent suspension of A or B red cells was added. After 30 minutes the tubes were centrifuged and examined for agglutination. A control tube contained no saliva and another control contained saliva of a known secretor. In the first control there was 4 plus agglutination and the same was found in the unknown when they were nonsecretors. In the case of secretors there was no agglutination, the testing serum having been neutralized by the blood group substance in the saliva. One or two plus agglutination was not common and a patient with such saliva was classified as a weak secretor. The concentration of A and B substance in plasma or serum was tested in the same manner.

The typing serum used for these tests was obtained from the Michael Reese Research Foundation. Diluted with saline the typing serum produced a trace of agglutination at 1:1000. The titer was not remarkably affected by cold. The serum contained isohemolysin as well as isoagglutinin.

Results

The plasma of 25 patients was examined for foreign antibodies immediately, and in most cases repeatedly, after receiving transfusions of group O blood. The results are shown in tables 1 and 2. In 10 of these patients there were no demonstrable foreign isoagglutinins after receiving transfusions ranging in volume from 2 to 14 pints. In the rest of the patients foreign antibodies were found immediately after the transfusion. No follow-up was possible in three cases. In five cases (including case D's anti-B) the foreign antibodies were not present after 1 day. In five cases (including D's anti-A) the antibodies persisted for 3 days or longer.

The transfused agglutinins were more easily demonstrable in the cold. The agglutinations tended to fall apart as the red cell suspensions were warmed, although when the titer of cold agglutination was high some clumping of the cells persisted at 37° C. (Table 3). Whole blood containing high titer of transfused agglutinins was incubated at 37° C. for 4 hours without hemolysis. Suspensions of test red cells in the serum of these patients incubated at 37° C. also gave no evidence of hemolytic activity. Direct Coombs tests on such blood were negative, indicating an absence of incomplete antibodies on the remaining native red cells (Table 1).

Table 1. Foreign Isoagglutinins After Transfusions of Low-Titer Universal Donor Blood

Patient	ABO Group	Secretor	Volume of Transfusion (Pints)	Isoagglutinin Titer (5° C.)	Disappearance Time of Isoagglutinins from Recipient's Blood	Direct Coombs Test
A	A	?	9	Trace	?	Neg.
B	A	No	20	1:64	10 days	Neg.
C	A	No	9	0		
D	AB	A no	15	Anti-A 1:128	9 days	
		B yes		Anti-B 1:2	3 hrs.	Neg.
E	A	No	8	0		Neg.
F	B	?	37	1:8	Died	
G	A	Weak	8	1:32	10 days	
H	A	Yes	7½ "high titer"	1:2	1 day	
I	A	Yes	13	0		Neg.
J	A	Yes	2	0		Neg.
K	A	Yes	7	0		
L	A	Yes	14	0		Neg.
M	A	Yes	9	1:4	1 day	
N	A	Yes	2	1:4	1 day	
O	A	Yes	2	0		
P	A	Weak	6	1:8	5 days	
Q	A	Yes	6	0		
R	B	Yes	2	0		
S	B	Yes	6	0		
T	AB	A no	2	Anti-A 1:8	Evacuated	
		B yes		Anti-B 0		
U	A	No	4	0		
V	A	Yes	3	0		
W	B	Weak	4	0		
X	A	Yes	22	1:2	12 hours	Neg.
Y	A	?	22	1:4	Died	
Z	A	Yes	3	0		

Table 2. Response to Large Transfusions of Group O Blood

Patient	ABO Blood Group	Date	Cumulative Total Blood Received (Pints)	Total RBC (10^6)	Inagglutinable RBC (10^6)	Proportion of Donor RBC (%)	Plasma Hemoglobin (mg./100 ml.)	Foreign Isoagglutinin (5° C.)	Reticulocytes (%)
A	A	14 Nov.	9	6. 66	4. 27	64	10	Trace	
		Postop.							
GSW: lacerations of bowel.		15 Nov.		5. 75	3. 59	62	4. 8		
		17 Nov.		5. 25	3. 40	65		0	
		19 Nov.		5. 21	3. 47	67	1. 1	0	
		24 Nov.		5. 10	3. 34	67	1. 6	0	
B	A	15 Nov. adm.	6	5. 0	3. 15	63	34	1:64	
Land mine: bilateral amputation of thighs.		Preop.	12				47	1:128	
		16 Nov.							
		Postop.	20	5. 07	4. 42	87	31	1:64	
		6 hr. postop.	20	4. 87	4. 77	98	2	1:32	
		12 hr. postop.	20	3. 95	3. 98	100	2. 3		
		17 Nov.	20	3. 705	3. 696	100	2. 8		
		19 Nov.	20	3. 1	3. 01	97		1:16	
		20 Nov.							
		Pre-tx	20	3. 53	3. 22	90	2. 5	1:16	
		Post-tx	22	3. 57	3. 59	100	2. 1	1:64	
		21 Nov.							
		Pre-tx	22	3. 79	3. 59	95		1:32	
		22 Nov.	24	4. 44	4. 42	99		1:32	
		23 Nov.	24	5. 12	4. 84	96		1:16	
		27 Nov.	24	4. 72	4. 52	96		1:4	
		29 Nov.							

		Pre-tx	24	5. 14	4. 41	86	2. 3	1:2	
		Post-tx	25	4. 57	4. 20	92	0. 9	1:4	
		4 Dec.	25	5. 23	4. 24	81		Trace	
		6 Dec.	25	5. 07	4. 08	80		Trace	
D	AB	21 Nov.							
GSW: lacerations, of bowel.		Postop.	14	8. 55	5. 49	64	35	1:128	
		22 Nov.		7. 81	5. 26	67	19		
		23 Nov.		6. 68	5. 42	81	21	1:128	
		24 Nov.		6. 65	5. 52	83	18	1:64	
		25 Nov.					14		
		26 Nov.		6. 68	5. 71	85	5. 2	1:64	
		27 Nov.		6. 84	6. 13	92	3. 9	1:16	
		29 Nov.		6. 81	5. 74	84	2. 3	1:8	
		1 Dec.		6. 69	5. 40	81		0	
		4 Dec.		7. 10	5. 41	76		0	
L	A	9 Dec. 26 hrs. post-op.	14	7. 47	6. 74	90	13. 2	0	
GSW: groin, transected femoral artery.		10 Dec.		7. 10	6. 80	96	7. 5		
		11 Dec.		6. 17	6. 06	98	1. 4	0	
		12 Dec.		6. 00	6. 00	100	0. 5		
		14 Dec.		6. 09	5. 80	95	0. 7	0	
		16 Dec.		5. 85	5. 24	90	0. 8	0	2
		22 Dec.		5. 33	4. 72	88	0. 6		1
		25 Dec.		5. 31	4. 54	85	0. 5		1. 5
X	A	5 Jan.							
Exploding flare: peroneum and retroperitoneum; clinical uremia.		Preop.	5	5. 13	2. 43	47			0. 7
		6 Jan. 4 hrs. postop.	15	4. 79	4. 0	82	39	Trace	0. 5
		15 hrs. postop.	17	4. 80	4. 17	87	7. 2	Trace	0. 6
		7 Jan.	18	4. 45	4. 11	92	4. 4	0	1. 4
		8 Jan.	18	3. 76	3. 45	92	2. 7	0	2. 0
		9 Jan.							
		Pre-tx	18	3. 60	3. 42	95	1. 3	0	2. 5

Table 2. Response to Large Transfusions of Group O Blood—Continued

Patient	ABO Blood Group	Date	Cumulative Total Blood Received (Pints)	Total RBC (10^6)	Inagglutinable RBC (10^6)	Proportion of Donor RBC (%)	Plasma Hemoglobin (mg./100 ml.)	Foreign Isoagglutinin (5° C.)	Reticulocytes (%)
		10 Jan.							
		Pre-tx	20	3.30	3.12	95	1.2	0	2.2
		11 Jan.	22	3.39	3.17	94		Trace	2.0
		12 Jan.	22	2.90	2.70	93	0.4	0	1.6
P GSW: pelvis and retroperitoneum.	A	14 Dec. adm.	0	4.7	0.014	0	1.6	0	
		Postop.	6	4.71	2.41	51	3	1:8	
		15 Dec.		4.43	2.50	56	0.8		
		17 Dec.		3.67	1.9	52	1.6	1:4	2.5
		20 Dec.		2.86	1.22	43	1.0	0	5.1
		22 Dec.		3.08	1.27	41	1.8	0	5.1
V Mortar: multiple wounds face, 4 extremities.	A	11 Dec. adm.	0	4.28	0.005	0		0	
		Postop.	3	4.21	1.71	25	11.5	0	
		12 Dec.		4.85	1.83	26	0.5	0	
		13 Dec.		4.30	1.50	28	0.6	0	
		15 Dec.		3.54	1.27	28	0.3	0	
		16 Dec.		3.41	1.23	28	1.1	0	3.4
S Grenade: multiple wounds amputation left leg.	B	22 Dec.							
		Preop.	4.5	5.06	2.81	55	3.9		1.5
		Postop.	6	5.14			4.6	0	1.1
		23 Dec.		3.61	2.42	67	0.9		3.6
		24 Dec.		3.51	2.07	59	2.8		4.4

Adm: on admission. Preop.: before operation. Post-tx: after transfusion. GSW: gunshot wound.

Table 3. Thermal Amplitude of Transfused Isoagglutinins

Patient	Blood Group	Anti-A Titer at 5° C.	At Dilution of 1:4				
			5° C.	15° C.	25° C.	30° C.	37° C.
B (postop.)	A	1:64	4+	3+	2+	+	+
B (after 4 days)		1:16	3+	+	Tr.	Neg.	Neg.
P (postop.)	A	1:8	3+	2+	+		Tr.
Y (postop.)	A	1:8	2+	+	Tr.	Neg.	Neg.
		Anti-B titer at 5° C.					
F (postop.)	B	1:8	2+	+	Neg.		

When patients of blood groups A and AB were transfused with moderate or large amounts of group O blood there was evidence of selective destruction of the patients' red cells (Table 2). In 10 of 14 patients on whom serial Ashby counts were performed, the proportion of donor cells increased for several days after the transfusion. Not all of these patients are shown in Table 2; data on the others have been published in another report.[6] Ebert and Emerson reported the same phenomenon in several casualties of World War II who received large transfusions.[8] Selective hemolysis of native red cells occurred in patients whose sera contained transfused isoagglutinins (B, D in Table 2) and also in those without foreign antibodies demonstrable in vitro (A, L, X). This manifested itself by an alteration of proportions of native and donor red cells. After the transfusion was concluded, the proportion of donor cells continued to increase while the native cells decreased. In two of these patients (D, L) the prolonged slight elevation of the plasma hemoglobin gave evidence of low-grade intravascular hemolysis. The destruction of the native red cells was not accompanied by a clinical reaction as has been described with transfusion of blood from dangerous universal donors.[9, 10, 12] The patients gave no outward sign of hemolytic disease.

Red cell destruction due to other mechanisms was also taking place.[6] During the 24 hours after transfusion of stored blood there was a modest loss of nonviable donor red cells that was often masked by the loss of recipient red cells (Table 2). In uremia associated with acute post-traumatic renal insufficiency hemolysis was often exceptionally rapid, affecting donor and recipient cells alike (Case X, Table 2). In the severely wounded there was evidence of hemolytic disease that destroyed donor and recipient red cells indiscriminately

(B, D in Table 2). This occurred in the early days of convalescence. The patients were usually evacuated from the surgical hospital within a week or two. Five of the patients whom we studied in Korea were transferred to Walter Reed Army Hospital where the Ashby counts were continued. It was found that the blood given at the time of wounding and initial resuscitation ultimately survived normally for 100 to 120 days, excepting in one man who was group A, Rh negative. In him the group O, Rh-positive cells survived 80 days. This is only a moderate reduction of survival time, although it is definitely abnormal. The patient did not have any evidence demonstrable in vitro of antibodies against Rh or other blood groups. This patient later developed hepatitis. A survey is under way to determine among the wounded the rate of sensitization against Rh and other blood group antigens as a result of transfusion with universal donor blood given without typing for Rh and other blood group antigens.

Massive transfusion and selective elimination of recipient red cells produced a replacement of red cells in two patients that approximated 100 per cent (B, L). In the Ashby preparations the agglutinated cells were so few in number and the agglutinations were so small that it was possible actually to count the agglutinated red cells. They comprised less than 1 per cent of the total. When reticulocyte strain was added to the Ashby suspension and the cells were then examined under high magnification it was seen that practically all of the agglutinated red cells were reticulocytes. None of the unagglutinated cells contained reticulum. The reticulocyte count became elevated in patients who developed anemia during convalescence (Table 2).

In three patients the secretor phenomenon was variable. When such a patient's saliva was tested just after resuscitation it did not completely inactivate the testing antiserum, although it did reduce the titer of the serum. When another specimen of the patient's saliva was tested several days later the amount of A substance had apparently increased (Table 4). This sort of patient was referred to as a "weak secretor." Where transfused isoantibodies persisted more than a day the patient was found to be a nonsecretor or weak secretor of the blood group substance in question (Table 1). Patient D, of group AB, was a secretor of B substance and a nonsecretor of A. He quickly eliminated anti-B agglutinins, but anti-A persisted in his plasma for 9 days.

Table 4. The Weak Secretor of a Substance

Patient	Dilution of Saliva						Saline Control	Nonsecretor Control 1:4
	1:4	1:8	1:16	1:32	1:64	1:128		
P (2 days postop.)	+	2+	------	------	------	------	4+	4+
P (4 days postop.)	0	0	Tr.	+	+	2+	4+	4+
Q (2 hours postop.)	0	0	Tr.	+	+	2+	4+	4+

Both patients had received plasma substitutes at the battalion aid station: P 500 ml. of gelatin; Q 1000 ml. of dextran. Both patients were group A and both received 6 pints of stored low-titer group O blood during resuscitation and surgery. For all of the above determinations the same typing serum and A red cells were used. The method is given in the text.

Nonspecific cold agglutinins active against group O red cells were noted at one time or another in most patients. The titer often seemed to be reduced after resuscitation and recovered during the period of convalescence. In only two patients did the titer exceed 1:16, which is considered to be the upper limit of normal for nonspecific cold agglutinins (Table 5).

Table 5. Titer of Nonspecific Cold Agglutinins Active Against Group O Red Cells

Patient	Before Surgery	After Surgery	Highest Titer During Convalescence
A		Tr.	1:2
B		0	1:8
D	0 (transfusion begun)	0	1:4
G	1:2 (transfusion begun)	0	1:8
H	1:4	1:16	1:64
I	1:2	0	Died
K	1:2	0	
L		1:8	1:64
M	0	0	1:8
N		0	1:4
P	1:2	Tr.	1:2
R	1:8	1:2	
Q	0	0	0
V	0	0	1:8
X		1:4	1:8

The transfused blood was cold. This may have something to do with the tendency of the titer of cold antibody to be low after surgery.

Discussion

The transfusion of large quantities of low-titer group O blood into patients of other groups did not produce an acute hemolytic reaction of the sort that has sometimes occurred with dangerous universal donors.[9, 10] However, it is clear from the evidence presented above that selective destruction of recipient red cells did occur, but the reaction was not abrupt or shocking.[6, 8] The selective destruction of recipient red cells was probably due to transfused isoantibodies. In several patients it was possible to demonstrate transfused isoagglutinins during the time that hemolysis was taking place (Table 2, Patient D). In other patients there were no isoagglutinins in the plasma, yet hemolysis of the patients' red cells occurred for several days after transfusion had been given. Patient L is an example. Patient X showed a less obvious reaction. There was no alteration of the proportion of donor to recipient red cells for several days. Most of the red cells in his blood were donor cells; only 5 to 8 per cent were his own. His reticulocyte count was slightly elevated, but all of the reticulocytes were native red cells. On January 9, for example, 2.5 per cent of the total red cells were reticulocytes and 5 per cent of the total were native red cells. Thus 50 per cent of the native red cells were reticulocytes. This suggested that the native red cells were being turned over at a very rapid rate, which implies selective destruction. In both L and X little or no isoantibody could be demonstrated against red cells of the patients' blood group, and the direct Coombs test was negative immediately after transfusion. This is reminiscent of hemolytic disease of the newborn when it occurs on the basis of an anti-A incompatibility. Transfused group A red cells are selectively eliminated from the infant's circulation, but the Coombs test is negative.[12] Apparently there are antibodies which we are incapable of detecting except by their pathogenic activity in vivo.

Where isoagglutinins against the patient's red cells persisted in his plasma it was, of course, impossible to cross match the patient's blood with red cells of his own hereditary group. This has been a problem of some clinical importance in Korea. Patients who become anemic during the early days of their convalescence were often transfused with fresh blood obtained from troops in the vicinity. On several occasions the use of group-specific blood has been associated with disastrous transfusion reactions.[6] It is suggested that the transfused isoantibodies persisting in the patient's plasma may react against the group-specific red cells when they are injected into the patient. Ervin and Young [10] have encountered transfusion reactions in patients of group A_2 who had been transfused, first with O blood and later with

A_1 blood. The reaction occurred because the patient had no A_1 antigen to neutralize the A_1 isoantibodies in the O blood. These antibodies, therefore, remained free and they reacted with the A_1 red cells at the second transfusion. This may have been the cause of the reactions that have happened uncommonly in Korea. Or they may have been due to the persistence of A_1 antibodies in A_1 patients following a heavy dose of transfused isoantibodies. As noted below, the persistence of A_1 antibodies did occur in A_1 patients. Whether or not this was pathogenic was not submitted to test by transfusing the patient with blood of his hereditary group. It was felt that regardless of the mechanism of the transfusion reaction the procedure was not justified: patients who had received large transfusions of group O blood should not receive blood of another group before sufficient time had elapsed to allow the foreign isoantibodies to disappear. It was recommended that if transfusions were needed meanwhile the use of group O blood should be continued.

The reason for the persistence of isoagglutinins in some patients and not in orthers is not entirely clear. There are two sides to the matter: the dose of antibodies in the transfused plasma and the capacity of the recipient to remove or neutralize those antibodies. All of the plasma given to the patients in the present study was of low titer, but the exact titer is not known. The expression low titer refers only to isoagglutinins active at room temperature. It does not refer to hemolytic or incomplete antibodies or to the sort that cause hemolysis in vivo without showing absorbed antibodies in vitro. The hemolysins and incomplete antibodies are of more pathogenic importance than the agglutinins.[9, 12] The agglutinin screen to identify high-titer blood is effective because a high titer of pathogenic antibodies is usually associated with a high titer of isoagglutinins. However, this is not always the case.[1] Group O blood may have a low titer of isoagglutinins and a high titer of isohemolysins or of incomplete antibodies or both. With the present screening procedures about 40 per cent of O blood is classified as high titer or potentially dangerous. It would be more economical if the proportion of high-titer blood could be reduced. There exists a need for a general re-evaluation of the problem of the universal donor and an appraisal of the different types of isoantibodies in his serum. Such a survey is in progress. Meanwhile, we are unable to define the dose of antibodies given the battle casualties beyond saying that all of the blood was of low agglutinin titer.

In several of the men the agglutinins persisted and were demonstrable in the plasma even though they represented an incompatibility, since not all of the native red cells had been eliminated. Other men who received a transfusion of similar size quickly cleared the agglutinins from the circulating plasma (Table 1). If we assume that comparable doses of agglutinin were given, it must follow that the patients differed from one another in their ability to dispose of the antibodies. The specific ability to neutralize isoantibodies resides in the blood group substances A and B. These substances are present on the red cells and in the circulating plasma. In some people they are also present in other tissues and body fluids. These people are called secretors because of the group substances found in their saliva, gastric juice, etc. One might suspect that the secretors, having A or B substance in more tissues than the nonsecretors, would be better able to neutralize transfused anti-A and anti-B. To some extent this appeared to be the case. The two patients who had a persistent high titer of foreign cold agglutinin were both nonsecretors (Table 1). Persistence of the agglutinin was also found in three weak secretors, patients in whom the concentration of A substance in the saliva was found to be considerably reduced after transfusion (Table 4). The persistence of anti-A agglutinin in an A subject was not an example of A_1 agglutinins in an A_2 subject. The native A cells in his blood formed hard agglutinations when suspended in his own cold serum. Furthermore, it was evident that the native red cells were selectively destroyed in vivo by the anti-A antibodies.

The failure of anti-B agglutinins to persist for long in any of the B or AB patients may have been fortuitous. There were few of them. B antibodies appear to be less troublesome than A. Perhaps they are more easily disposed of. The reactions that follow the transfusion of high-titer anti-B plasma are less severe than those encountered with the same titer, or less, of anti-A.[15] People appear to differ in their ability to cope with the transfused incompatible isoantibodies. Perhaps the blood of the "dangerous universal donors" is especially dangerous to those whose protective shield of soluble A substance is a weak one.

The nature of the transfused antibodies that persisted in the plasma of these patients was examined. No hemolysins were detected. This is not surprising because, as Ervin, Christian, and Young have noted, the isohemolysin is the form of isoantibody most readily neutralized by the soluble blood group substances.[9] Also, the direct Coombs test was negative in our patients. This is in agreement with the observations on hemolytic disease of the newborn when it is due to anti-A activity against the red cells of the infant: the Coombs test may be negative but group A red cells are rapidly destroyed in vivo.[12] In the present series the isoagglutinins were the only form of foreign antibody that could be demonstrated in the plasma of the recipients. Anti-A and B agglutination is known to be more effective in the cold.[11] The isoagglutinins of the ABO system exist as both warm and cold agglutinins. The isoantibodies transfused into these patients were of all varieties: warm and cold agglutinins, hemolysins incomplete antibodies, and others that caused hemolysis in vivo but ,could not be demonstrated in vitro. This last type of antibody tended to persist and cause selective destruction of the native red cells. Incomplete antibodies and classical hemolysins disappeared quickly. Warm agglutinins were demonstrable in patients whose serum showed a high titer of foreign cold agglutinins (Table 3). As the titer declined after the transfusion it was possible to demonstrate agglutination only in the cold.

The pathogenicity of isoagglutinin anti-A is open to question.[9, 12] Where reactions to the plasma of dangerous universal donors have occurred, it seemed that isohemolysins and incomplete antibodies were the important ones.[9] Patient B (Table 2) provides similar evidence. Almost 100 per cent of his red cells had been replaced by group O donor cells during his original transfusion. Because of anemia his bone marrow produced red cells at an increased rate and by November 20, 10 per cent of the total red cells were his own. In spite of anti-A agglutinins present at a titer of 1:16, these group A red cells were able to exist in his circulation. (In undiluted serum the agglutination of A cells, including the 10 per cent of the patient's own red cells, was 4 plus.) On that day, because of anemia, the patient was given 2 pints of fresh, group O blood locally procured. The 10 per cent of native group A red cells immediately disappeared from his blood stream. The titer of cold agglutinins increased by 2 tubes, but it is possible that other more destructive anti-A antibodies contributed to the loss of native A red cells.

A selective loss of the recipient red cells was not the only process of red cell destruction in these patients. Three other hemolytic mechanisms were identified. One was the loss of nonviable red cells present in the bank blood. A second was the hemolytic disease that appeared in patients who developed uremia on the basis of acute post-traumatic renal insufficiency. Patient X developed clinical uremia rather late in the course of his convalescence. The fall in red cell count of 500,000 during a 24-hour period January 11 to 12 was probably related to uremia (Table 2). A third hemolytic process was observed in the most severely wounded whose wounds involved damage or destruction of large masses of tissue. Patient B, for example, had a bilateral traumatic amputation of the thighs. He was given 20 pints of blood during resuscitation and surgery. He was not in shock. On the basis of computed loss and measured blood volume we were unable to account for 8 pints of blood immediately after the operation.[6]

Subsequently, he became progressively anemic although very little blood oozed from the stumps of his thighs. We believe that a hemolytic disease was present in such patients, but the mechanism is not known. Donor and recipient cells were lost indiscriminately.

The etiology of post-traumatic renal insufficiency is obscure. It has been suggested that hemoglobin liberated during the massive transfusions might play a role. It will be seen in Table 3 that the amounts of plasma hemoglobin encountered during and after such transfusions are not great and certainly not of the order of magnitude (800 to 2,000 mg. per 100 ml.) shown to be pathogenic in shocked dogs.[13] We were unable to correlate hemoglobinemia with the appearance of acute renal insufficiency. It is true that the two are associated in severe hemolytic transfusion reaction. In Korea all patients who developed actute renal insufficiency were evacuated to the Renal Insufficiency Center at the 11th Evacuation Hospital. In 1952 only 4 patients out of 74 admitted to that Center had a history or evidence of post-transfusion hemoglobinuria. Each of the four had been given group-specific blood that was locally procured. In two cases there had apparently been an error of blood grouping. The other two had been given large transfusions of group O blood and were then switched to group-specific blood.[14] So far as we know there have been no hemoglobinuric transfusion reactions due to transfusions of low-titer group O blood into recipients of other groups. During the present work of the Surgical Research Team in Korea, the minor side incompatibility has not been shown to be harmful. Nor was there any statistical evidence of renal injury by group O blood among the casualties of the Italian campaign in World War II. The incidence of hemoglobinuric nephrosis was not higher in men of blood group A than it was in group O where the minor side incompatibility did not exist.[2]

Summary

1. Following large transfusions of low-titer group O blood into patients of group A, B, and AB it was not possible to demonstrate foreign isohemolysins or incomplete antibodies in the serum of recipients. Cold isoagglutinins were frequently demonstrated immediately after the transfusion, but they usually disappeared rapidly. In several patients the titer of foreign anti-A isoagglutinin was quite high and the antibody persisted in the circulation for several days. It was suggested that the persistence of these agglutinins may have been possible because there was a relatively small amount of A substance in the body of the recipient. Where the transfused isoagglu-

tinins persisted the patients were found to be nonsecretors or weak secretors of A substance in the saliva.

2. In most of these patients there was evidence of a selective destruction of recipient red cells after the transfusion of O blood. This was probably due to the activity of transfused isoantibodies in the plasma of the O blood. This hemolytic activity was observed where it was not possible to demonstrate the presence of foreign isoantibodies. It is suggested that there may exist forms of antibody that cannot be demonstrated by laboratory methods. These antibodies manifest themselves only by causing destruction of red cells in vivo.

3. Clinically the hemolytic disease on the basis of such transfused isoantibodies while causing destruction of native red cells did not threaten the lives or impede the recovery of these patients. No reactions were encountered and none were heard of in Korea that might have been ascribed to a dangerous universal donor. The partition of group O blood into high titer and low titer on the basis of dilution of 1:200 to 1:256 has proved in practice to be safe.

4. The persistence of foreign antibodies after a large transfusion of group O blood may make it impossible to cross match the patient's blood with blood of his hereditary group. Severe transfusion reactions have occurred when group-specific blood has been given following large transfusions of group O blood. It has been recommended that after a large transfusion of group O blood has been given, group-specific blood should not be used for at least 2 weeks.

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Chapter 8

Changes in the Coagulation Mechanism Following Wounding and Resuscitation with Stored Blood*

A Study of Battle Casualties in Korea

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During the summer and autumn of 1952 a study of hepatic function in battle casualties was carried out by the Surgical Research Team of the U. S. Army in Korea.[11] The observations were made at a forward Surgical Hospital 1 to 4 hours after wounding, at the time of initial resuscitation and surgery and during the first days of convalescence. The one-stage prothrombin time was employed as one index of hepatic function. It was observed that following wounding and resuscitation with stored blood, prothrombin activity fell to about 50 per cent of normal. This was followed, within 4 days, by a return toward normal which persisted 1 to 3 days. Following this rise, prothrombin activity again fell. In some of the most severely wounded the "primary rise" toward normal was small or absent, and the "primary fall" and "secondary fall" blended into one period of decreased prothrombin activity before the late rise to normal began on about the tenth day. It was the purpose of the present study to define these changes in prothrombin activity.

Methods and Materials

During the winter of 1952–1953 a total of 11 moderately and severely wounded battle casualties were studied in detail, 7 from the immediate postoperative period, the remainder from the first postoperative day until evacuation 4 to 10 days later. These patients had received 6 to 16 pints of stored whole blood 10 to 15 days old. The daily tests consisted of clotting time, platelet count, plasma fibrinogen, and one-stage prothrombin time. On days that significant changes in prothrombin activity were noted three additional tests were carried out to determine the effect of the patients' plasma on the prothrombin time of stored plasma and to determine the effect of deprothrombinized plasma and heated serum on the patients'

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plasma. An additional 16 patients had prothrombin time determinations only. This group had received 5 to 30 units of blood.

Prothrombin time was determined by the one-stage method of Quick,[9] adding calcium and then thromboplastin to 0.1 ml. of oxalated plasma. The determination was carried out in duplicate or triplicate. The variation between determinations on any given specimen was usually 0 to 0.1 second, rarely greater than 0.2 second, and 0.3 second was considered the maximal allowable variation. Meticulous care in every detail was employed in standardizing the test. All of the determinations were carried out by one of the authors (RS).

Thromboplastin was of human brain origin prepared by the standard acetone extraction technic.[9] The prothrombin time of normal plasmas varied from 9.8 to 11 seconds with one lot of thromboplastin and from 11 to 12.6 seconds with another lot.

Calcium chloride, 0.015 M, was used in the volume that was found to give the shortest prothrombin time for each plasma tested. The volume of calcium chloride solution added was varied by 0.01 ml. until the optimal amount was determined. It was found that a patient with a low hematocrit usually required less calcium than a patient with a high hematocrit. The usual volume of calcium chloride solution required was $0.1 \pm .02$ ml.

Diluent for establishing the curve for normal prothrombin activity was prepared by incubating normal oxalated plasma with 0.008 M tricalcium phosphate gel.[9] Residual prothrombin activity of this plasma was less than 1 per cent (Table 1, tube 12). Gel-treated plasma is free of prothrombin and stable factor but contains the original labile factor.[2–4] It is referred to below as "deprothrombinized plasma."

Stored plasma was prepared by storing normal, sterile oxalated plasma at 4° C for 4 weeks in an unsealed container. It had a prothrombin time of about 26 seconds (Table 1, tube 9). Plasma so treated is deficient in labile factor.[9] When one part of normal oxalated plasma was added to nine parts of stored plasma the deficiency was partially corrected and the prothrombin time decreased from 26 seconds to about 15 seconds (Table 1, tubes 9–10).

Table 1. Characterization of Reagents Prepared From Normal Blood

Tube	Oxalated Plasma (ml.)	Deprothrombinized Plasma (ml.)	Stored Plasma (ml.)	Heated Serum (ml.)	Prothrombin Time (Seconds)
1	0. 10				12. 0
2	0. 08	0. 02			13. 1
3	0. 05	0. 05			15. 0
4	0. 03	0. 07			18. 8
5	0. 02	0. 08			22. 2
6	0. 09	0. 01			12. 4
7	0. 09			0. 01	12. 4
8		0. 05		0. 05	No clot
9			0. 10		26. 4
10	0. 01		0. 09		15. 4
11			0. 09	0. 01	27. 5
12		0. 10			90. 0
13	0. 1	(No brain thromboplastin added).		0. 10	No clot

Note. In tubes 1 to 12 the prothrombin time was taken after adding first calcium and then thromboplastin.

Plasma free of stable factor (Factor VII) was prepared by filtering oxalated ox plasma through 30 per cent asbestos filter pads.[7]

Heated serum was prepared by adding 5.0 ml. of freshly drawn blood to 0.2 ml. of active thromboplastin solution. The blood coagulated instantly and was then incubated for 30 minutes at 37° C. This treatment was found to convert all prothrombin to thrombin and all labile factor to activated labile factor. The serum was decanted and 2.8 ml. were oxalated by adding 0.5 ml. of 0.1 M potassium oxalate. Finally it was incubated at 53° C. for 30 minutes. Heated serum used as a diluent prolonged the prothrombin time of normal plasma (Table 1, tubes 1 and 7). It did not cause deprothrombinized plasma to clot (Table 1, tube 8). These observations indicated that the heated serum contained no thrombin or prothrombin. Heated serum did not cause clotting of ox plasma that was free of stable factor. This indicated that heated serum did not contain stable factor. Heated serum prolonged the clotting time of stored plasma (Table 1, tubes 9 and 11). This indicated that heated serum did not contain labile factor. Heated serum when used in the place of thromboplastin in a one-stage test did not cause normal plasma to clot (Table 1, tube 13). This indicated that heated serum did not contain thromboplastin.

The serum at 56° C. did not form a coagulum. This indicated that no fibrinogen was present in heated serum.

Fibrinogen determinations were carried out using Quick's modification of the method of Cullen and Van Slyke.[9] Twenty normal plasmas varied from 225 to 400 mg. per 100 ml.

Clotting time was carried out using a modification of the method of Lee and White.[10] Siliconed (Desicote) tubes and syringes were used throughout. After venipuncture the syringe was changed to draw the blood, obviating contamination with tissue juices. A stop watch was started when blood appeared in the syringe. Clotting time of normal blood varied from 25 to 40 minutes.

Platelet counts were determined using the method of Brecher and Cronkite.[1] The normal platelet count varied between 200,000 and 300,000 per cu. mm.

Calculation of Results

So that changes could be studied and presented graphically the following system was followed.

Prothrombin activity was stated as per cent of normal activity. By diluting normal plasma with normal deprothrominized plasma, the prothrombin time at several concentrations was established. Prothrombin time was plotted against concentration on logarithmic graph paper, and the patient's activity was calculated from this curve (Table 1, tubes 1–5).

The effect of heated serum and deprothrombinized plasma on patient's plasma was calculated as follows (for example, Patient DD, Table 2):

The deficit of prothrombin activity of undiluted plasma was determined.

Activity of normal undiluted plasma	100 per cent	
Activity of patient's undiluted plasma	—66 per cent	
Per cent deficit of undiluted plasma	34 per cent	(A)

Table 2. The Effect of Deprothrombinized Plasma on the Prothrombin Time of Patient's Plasma During the Primary Fall

Patient.* Size of Transfusion. Type of Wound.	Oxalated Plasma (ml.)**	Deprothrombinized Plasma (ml.)	Prothrombin Time (Seconds)	Prothrombin Activity (Per Cent of Normal)	Correction of Coagulation Defect (Per Cent)
DD–15					
Perforation of chest and lung	N–0.1	0	11. 4	100	
	N–0.02	0. 08	19. 8	20	
	P–0.1	0	13. 2	66	
	P–0. 02	0. 08	21. 0	18	70
EE–9					
Penetrating wounds of both legs; traumatic	N–0.1	0	10. 6	100	
	N–0.01	0. 09	27. 0	10	
	P–0.1	0	12. 8	80	
	P–0.01	0. 09	33. 6	8	0
M–6					
Penetrating wound of chest, diaphragm and liver	N–0.1	0	12. 0	100	
	N–0.02	0. 08	20. 4	20	
	P–0.1	0	14. 6	62	
	P–0.02	0. 08	25. 5	12	0
FF–9					
Penetrating wound of abdominal walls and back	N–0.1	0	12. 0	100	
	N–0.01	0. 09	26. 8	10	
	P–0.1	0	13. 2	80	
	P–0.01	0. 09	28. 5	8	0
X–16					
Extensive injury of buttocks	N–0.1	0	10. 4	100	
	N–0.09	0. 01	11. 0	90	
	P–0.1	0	13. 7	48	
	P–0.09	0. 01	13. 6	48	10
GG–13					
Penetrating wounds of extremities, large and small intestine	N–0.1	0	12. 2	100	
	N–0.04	0. 06	14. 5	40	
	P–0.1	0	13. 8	55	
	P–0.04	0. 06	17. 4	28	33

*The identifying letters are the same as those used in two other reports dealing with this same group of patients.[3, 4] The number is volume of transfusion in pints of blood.

**N = Normal Plasma. P = Patient's Plasma.

Prothrombin activity of patient's and normal plasmas at a given dilution was determined after diluting the plasmas with heated serum or deprothrombinized plasma. The deficit of prothrombin activity at that dilution was then established (DD, Table 2).

At 20 per cent dilution normal plasma activity=20 per cent.

At 20 per cent dilution patient's plasma activity=18 per cent.

Activity of the patient's plasma in terms of normal at that dilution= $\frac{18}{20}$ or 90 per cent activity.

The deficit at that dilution=100 minus 90 or 10 per cent (B).

The correction of the coagulation defect by the diluent can be calculated:

$$\frac{A=B}{A}\times 100=\frac{34-10}{34}=70 \text{ per cent Correction}$$

Effect on stored labile factor deficient plasma was calculated on a logarithmic curve constructed in a fashion similar to that used for the one-stage prothrombin time.

Results

A primary fall of prothrombin activity to about 50 per cent of normal was observed immediately after surgery and persisted 1 to 4 days. This is referred to as the "primary fall." In 70 per cent of 28 cases, the maximal depression had been found to occur immediately postoperatively and varied from 34 to 80 per cent of normal.[11] This was followed by a "primary rise" to 90 per cent of normal activity or higher during the first 4 postoperative days. On the third to the fifth day there was "secondary fall" to 50 per cent of normal activity which persisted until the tenth postoperative day before a return to normal activity began. The maximal fall usually occurred about the seventh day and varied from 20 to 80 per cent of normal activity.

Observations During the Primary Fall

1. In three of six cases the addition of defibrinized plasma to patient's plasma caused some correction of coagulation defect in the one-stage test (Table 2). This occurred in the three patients who had the largest transfusions.

2. In all of four cases the patient's plasma had less than normal ability to correct the coagulation defect of stored plasma (Table 3). This defect of patient's plasma was most pronounced in the immediate postoperative period and was less pronounced as the one-stage prothrombin time rose to normal between the first and third days.

Table 3. The Effect of Patient's Plasma on the Prothrombin Time of Stored Plasma During the Primary Fall

Patient. Size of Transfusion. Type of Injury.	Oxalated Plasma (ml.)*	Stored Plasma (ml.)	Prothrombin Time (Seconds)	Labile Factor Activity (Per Cent of Normal)
DD–15				
Perforation of chest and lung		0. 10	26. 5	
	N–0. 01	0. 09	18. 7	100
	P–0. 01	0. 09	20. 4	78
EE–9				
Penetrating wounds of both legs; traumatic amputation of left leg		0. 10	26. 2	
	N–0. 01	0. 09	17. 2	100
	P–0. 01	0. 09	18. 4	82
M–6				
Penetrating wound of chest, diaphragm and liver		0. 10	26. 0	
	N–0. 01	0. 09	17. 6	100
	P–0. 01	0. 09	20. 6	70
X–16				
Extensive injury of buttocks		0. 10	25. 2	
	N–0. 01	0. 09	15. 0	100
	P–0. 01	0. 09	20. 8	56

*N=Normal plasma. P=Patient's plasma.

3. When heated serum was added to patient's plasma during the immediate postoperative period there was no correction of the coagulation defect. The prothrombin time was prolonged as though the heated serum were a simple diluent. As the "primary rise" to normal prothrombin activity began, the heated serum was partially able to correct the residual defect of coagulation in the one-stage test.

Observations During the Secondary Fall

1. In all of nine cases the addition of normal heated serum to the one-stage test of the patient's plasma corrected to some extent the defect of coagulation. Heated serum of such patients did not correct the defect when added to their own plasma or the plasma of patients at a similar stage of recovery (Table 4).

2. The ability of the plasma of these patients to correct the defect of stored plasma was even better than normal (Table 5).

Table 4. Effect of Heated Serum on the Prothrombin Time of Patient's Plasma During the Secondary Fall

Patient. Size of Transfusion. Type of Injury.	Oxalated Plasma (ml.)*	Heated Serum (ml.)	Prothrombin Time (Seconds)	Prothrombin Activity (Per Cent of Normal)	Correction of Coagulation Defect (Per Cent)
DD–15					
Perforation of chest and lung	N–0.10		10. 9	100	
	N–0.09	0. 01	11. 3	90	
	P–0.10		13. 2	64	
	P–0.09	0. 01	12. 4	72	44
EE–9					
Penetrating wounds of both legs; traumatic amputation of left leg	N–0.10		11. 2	100	
	N–0.09	0. 01	11. 5	90	
	P–0.10		12. 8	70	
	P–0.09	0. 01	11. 7	89	98
M–6					
Penetrating wound of chest, diaphragm and liver	N–0.10		12. 8	100	
	N–0.09	0. 01	13. 3	90	
	P–0.10		13. 7	78	
	P–0.09	0. 01	13. 4	90	100
FF–9					
Penetrating wound of abdominal walls and back	N–0.10		10. 8	100	
	N–0.09	0. 01	11. 2	90	
	P–0.10		12. 4	78	
	P–0.09	0. 01	11. 8	82	59
X–16					
Extensive injury of buttocks	N–0.10		9. 2	100	
	N–0.09	0. 01	9. 5	90	
	P–0.10		10. 4	80	
	P–0.09	0. 01	10. 3	80	45
L–14					
Perforation of iliac artery	N–0.10		12. 6	100	
	N–0.09	0. 01	12. 9	90	
	P–0.10		15. 0	47	
	P–0.09	0. 01	14. 0	57	30
GG–13					
Penetrating wounds of extremities, large and small intestine	N–0.10		10. 1	100	
	N–0.09	0. 01	10. 6	90	
	P–0.10		12. 0	60	
	P–0.09	0. 01	12. 1	60	17
LL–9					
Penetrating wounds of kidney, colon, bladder and extremity	N–0.10		10. 4	100	
	N–0.09	0. 01	11. 0	90	
	P–0.10		11. 8	72	
	P–0.09	0. 01	11. 6	74	36

*N = Normal Plasma. P = Patient's Plasma.

Table 5. Effect of Patient's Plasma of the Prothrombin in Time of Stored Plasma During the Secondary Fall

Patient. Size of Transfusion. Type of Wound.	Oxalated Plasma** (ml.)	Stored Plasma (ml.)	Prothrombin Time (Seconds)	Labile Factor Activity (Per Cent of Normal)
DD–15				
Perforation of chest and lung		0. 10	25. 0	
	N–0.01	0. 09	17. 2	100
	P–0.01	0. 09	16. 2	113
EE–9				
Penetrating wounds of both legs; traumatic amputation of left leg		0. 10	25. 0	
	N–0.01	0. 09	17. 8	100
	P–0.01	0. 09	15. 8	128
M–6				
Penetrating wound of chest, diaphragm and liver		0. 10	25. 0	
	N–0.01	0. 09	17. 8	100
	P–0.01	0. 09	14. 8	141
FF–9				
Penetrating wound of abdominal walls and back		0. 10	26. 4	
	N–0.01	0. 09	16. 9	100
	P–0.01	0. 09	13. 6	135
X–16*				
Extensive injury of buttocks		0. 10	28. 0	
	N–0.01	0. 09	14. 2	100
	P–0.01	0. 09	15. 4	92
L–14				
Perforation of iliac artery		0. 10	24. 0	
	N–0.01	0. 09	17. 8	100
	P–0.01	0. 09	17. 8	100
GG–13*				
Penetrating wounds of extremities, large and small		0. 10	28. 0	
	N–0.01	0. 09	14. 2	100
	P–0.01	0. 09	17. 0	80

**N = Normal plasma. P = Patient's plasma.

*Severely wounded with complicated recovery.

3. The addition of deprothrombinized plasma to patient's plasma failed to cause the anticipated prolongation of the patient's prothrombin time. In all six of the patients tested (Table 6) there was

evidence to indicate that normal deprothrombinized plasma tended to correct the coagulation defect of the patient's plasma in the one-stage test. When normal deprothrombinized plasma was used to dilute normal plasma and the plasma of patients in the secondary fall, the two dilution curves crossed, so that in some cases the prothrombin time of the patient's plasma at high dilutions was actually shorter than that of normal plasma at the same dilution (Table 6, L–14).

Fibrinogen (Fig. 1). Only one patient in the study group had an abnormally low fibrinogen, but the value was not low enough to affect coagulation (182 mg. per 100 ml.). This occurred after operation and had corrected itself by the first postoperative day. The average postoperative value was 233 mg. per 100 ml. and rose to an average of 423 mg. per 100 ml. by the first day. The average maximum value, 653 mg. per 100 ml., occurred between the third and eighth days.

Clotting Time in Silicone (Fig. 1). Six of seven patients studied in the immediate postoperative period had clotting times of 13 to 20 minutes which were more rapid than normal. Six of ten patients had a normal clotting time by the first postoperative day. In four the clotting became abnormally prolonged. Of these, two returned to normal on the third and fifth days. The other two remained abnormal during their entire hospital stay of 4 and 6 days respectively. One of the latter developed lower nephron nephrosis and demonstrated a bleeding tendency on the third and fourth day, but with no abnormality of platelet count, fibrinogen, or prothrombin activity that would account for the prolonged clotting time. In general, clot reaction was normal. Some patients who had been overtransfused and had a high hematocrit appeared to have poor clot retraction.

Table 6. The Effect of Deprothrombinized Plasma on the Prothrombin Time of Patient's Plasma During the Secondary Fall

Patient. Size of Transfusion. Type of Wound.	Oxalated Plasma* (ml.)	Deprothrombinized Plasma (ml.)	Prothrombin Time (Seconds)	Prothrombin Activity (Per Cent of Normal)	Correction of Coagulation Defect (Per Cent)
M–6					
Penetrating wound of chest, diaphragm and liver.	N–0.1		12. 8	100	
	N–0.09	0. 01	13. 4	90	
	P–0.01		13. 7	85	
	P–0.09	0. 01	13. 2	90	100
FF–9					
Penetrating wound of abdominal walls and back.	N–0.1		11. 9	100	
	N–0.09		12. 2	90	
	P–0.1		12. 2	90	
	P–0.09	0. 01	12. 2	90	100
L–14					
Perforation of iliac artery.	N–0.1		12. 0	100	
	P–0.1		13. 1	80	
	N–0.08	0. 02	13. 1	80	
	P–0.08	0. 02	13. 1	80	100
	N–0.02	0. 08	22. 2	20	
	P–0.02	0. 08	19. 0	27	100+
GG–13					
Penetrating wounds of extremities, large and small intestine.	N–0.1		9. 8	100	
	N–0.09	0. 01	10. 2	90	
	P–0.1		12. 0	60	
	P–0.09	0. 01	11. 8	63	25
LL–9					
Penetrating wounds of kidney, colon, bladder, and extremity.	N–0.1		10. 4	100	
	N–0.09	0. 01	11. 0	90	
	P–0.1		11. 8	78	
	P–0.09	0. 01	11. 6	76	33

*N = Normal plasma. P = Patient's plasma.

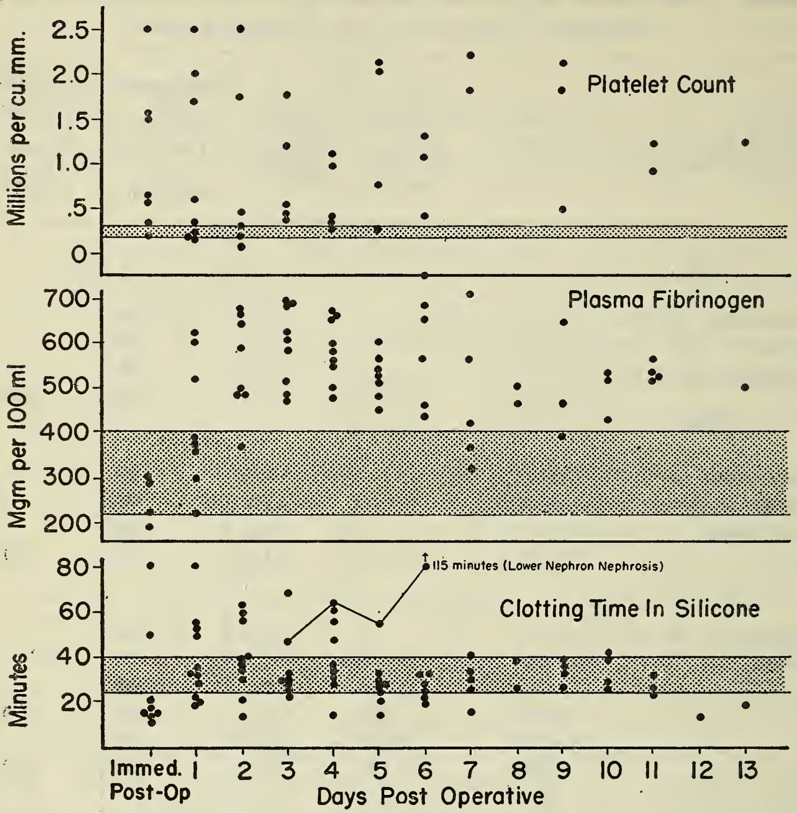

FIGURE 1. Daily changes in clotting time, plasma fibrinogen and platelet count in 11 casualties who were severely wounded. Two platelet counts on the fourth and fifth days have been omitted. One was 4.2 million, the other 3.2 million per cu. mm.

Platelets (Fig. 1). No patients in this group had a fall in platelets that could cause a hemorrhagic tendency. Only one patient had low platelet count immediately postoperatively (190,000 per cu. mm.), and this was corrected by the second postoperative day. One other patient had a low count (170,000 per cu. mm.) on the first day postoperatively, following continued transfusion of stored blood. It became normal the next day. In most of the patients after operation the platelet count rose well above normal and reached a peak between the third and ninth day. The maximum counts varied from 0.48 to 4.2 million per cu. mm.

Discussion

The changes in one-stage prothrombin activity observed in these patients are small, but the method was carefully controlled. It is believed that the changes are significant. Alteration of prothrombin activity after surgical operations has been described by Stefanini[12] and by Warren and Belko.[13] Stefanini ascribed the fault to a lack of labile factor. Warren and Belko indicated that it was due to a lack of "coagulation accelerators." Our own observations indicate that the primary fall was caused, in part at least, by a lack of labile factor. The secondary was due to lack of something else. Many factors can modify the one-stage prothrombin time. Some are known, and these include prothrombin, labile factor (labile component, Factor V, proaccelerin, plasma Ac-globulin), stable factor (proconvertin, Factor VII), antihemophilic globulin and similar factors, the platelet factors, anti-thrombin and heparin.[12] There may be others that are still unknown.

It seems improbable that the coagulation defect in the severely wounded was due to an anticoagulant. Six of ten patients studied had a normal clotting time by the first postoperative day and it is safe to assume that no anticoagulant was present in these patients. Previous authors have reported a fall in clotting time after stress.[2] Four of the ten patients did have abnormally prolonged clotting times past the first day. These patients had changes of prothrombin activity of the same degree as did patients with normal clotting times. The abnormal clotting time in these four patients could have been on the basis of some inhibitor but this was not proven. However, it was shown that these patients had, in addition, the same abnormality of prothrombin conversion that was possessed by the other six patients who had a normal clotting time.

There was no lack of fibrinogen to account for the coagulation defect. A rise in plasma fibrinogen following injury has been reported previously.[5] It is interesting to note that this response does occur in a severely wounded casualty who is in a state of severe negative nitrogen balance. Two of the casualties were polycythemic from "overtransfusion"; neither of these patients demonstrated depression of the fibrinogen associated with polycythemia vera.

The status of prothrombin itself is open to question. In some patients it was possible to correct the prothrombin time to normal (or even better) by the addition of deprothrombinized plasma or heated serum that contained no prothrombin. This suggested that there was little or no lack of prothrombin in these patients. In other patients, where the use of prothrombin-free reagents improved but did not correct completely the defect in coagulation, there may have been some deficiency of prothrombin. It is noteworthy that the use of vitamin K (100 mg. daily, intramuscularly) on five patients did not correct the defect in either the primary or secondary fall of prothrombin activity. Vitamin K–1 oxide was not tested.

The optimal concentration of calcium required for the one-stage prothrombin time was established each day for each patient. Immediately after large transfusions of citrated blood the amount of calcium required was no greater than was required for the normal control and no greater than was required for the same patient on the succeeding days, provided the hematocrit remained the same. This suggested that the citrate did not produce any great alteration of physiologically available calcium in the plasma of these patients. Clinical observation suggested the same, because hypocalcemic tetany was not encountered in these patients.

Labile factor appears to have been deficient during the primary fall. The labile factor deficiency of stored plasma was not well corrected by the addition of patient's plasma to stored plasma. At the same time the coagulation defect in three of the six patients could be corrected by adding deprothrombinized plasma which contains labile factor but not stable factor or prothrombin. The lack of labile factor, in the postoperative period, may have been due to the large transfusions of bank blood which these patients received. All of the blood was more than 10 days old, and it has been shown that blood stored in ACD solution becomes relatively deficient in labile factor.[8] It should be stated, however, that the coagulation defect was not so great as to cause a serious fault of hemostasis. The slight oozing tendency that occurred among battle casualties after transfusion of 20 pints of blood or more was probably not on the basis of the labile factor deficiency of the degree demonstrated. We also found that it was not due to fibrinolysis or a deficient number of platelets. It may have been caused by some vascular phenomenon or plethora but not all patients with the oozing tendency were polycythemic. The phenomenon was observed in patients who were shown to be anemic from blood loss. The platelet factor, "serotonin,"[6] acts upon capillaries to cause vasoconstriction at the site of the capillary damage. It should be pointed out that these severely wounded patients had received a virtual replacement transfusion with blood containing nonviable platelets. Since their platelet counts did not fall they must have produced large numbers of platelets in a relatively short time. It is possible that the immature platelets were deficient in "serotonin," or some other platelet factor of hemostatic importance. Such a deficiency could predispose to oozing. The oozing was of no clinical importance.

The "secondary fall" of prothrombin activity presents a problem we cannot explain. At this stage of recovery the coagulation defect of the one-stage prothrombin test was corrected by the addition of heated serum that was free of fibrinogen, labile factor, stable factor, prothrombin and thrombin. The defect was also corrected by deprothrombinized plasma, which indicates that the deficient factor was not absorbed by tricalcium phosphate gel. The factor or factors that corrected the "secondary" coagulation defect were stable in oxalated serum heated to 53° C for 30 minutes. It was found to withstand a temperature of 56° C for the same period of time. Its heat stability and its failure to be absorbed by tricalcium phosphate gel are two characteristics that eliminate all of the known clotting factors excepting the Platelet Factor 3.[12] It should be mentioned that at this phase of recovery the patients were producing excessive numbers of platelets (Fig. 1), many of which were large and immature. It is possible that, because of rapid production of platelets, a deficiency of Platelet Factor 3 could exist. This deficiency may not have been apparent earlier, immediately after the transfusion, because of the contribution of platelet materials from the large numbers of nonviable platelets in the transfused blood or because the production mechanism of this factor had not as yet failed. There appeared to be no lack of labile factor during the secondary fall. The patient's plasma was usually more than adequate to correct the coagulation defect of stored plasma (Table 5). There appeared to be no lack of prothrombin in the patient's plasma. The addition of heated serum or deprothrombinized plasma restored the prothrombin times that were prolonged more quickly than normal (Tables 4 and 6). It is not assumed that a deficiency of Platelet Factor 3 has been demonstrated in these patients. The fault in the coagulation mechanism may have been due to lack of a heat-stable plasma factor (Toch'on-ni factor) that has not yet been described.

Summary and Conclusion

1. The coagulation system was studied in 11 battle casualties immediately after they had been wounded and resuscitated and during the first days of their convalescence.

2. In general the clotting time was shorter than normal and the platelet count and fibrinogen concentration were greater than normal. Prothrombin activity as measured by the one-stage test averaged 50 per cent of normal immediately after resuscitation with large transfusions of stored blood. This defect corrected itself within 1 to 3 days, but about the fourth day prothrombin activity again was reduced to about 50 per cent of normal and thereafter recovered gradually.

3. The primary fall of prothrombin activity was not proved to be caused by a lack of prothrombin but appeared in some cases to be related to a lack of labile factor which may have been a consequence of large transfusions of stored blood deficient in the labile factor. The prothrombin time was not always corrected by addition of labile factor. The defect of the coagulation mechanism was never great enough to cause serious hemorrhage. A tendency to ooze was noted in patients who had received over 20 pints of blood in a short time. It is suggested that this may have been due to the presence of a great number of immature platelets in the circulation. No fibrinolytic reactions were observed.

4. The secondary fall of prothrombin activity was not due to the lack of prothrombin. The defect of the coagulation mechanism could be corrected by the addition of heated serum that was free of prothrombin, thrombin, labile factor, stable factor, and thromboplastic activity. The factor responsible for the correction of the coagulation defect was heat stable (56° C. for 30 minutes in the presence of oxalate) and was not absorbed by tricalcium phosphate gel. Of the known factors involved in the coagulation system, these two characteristics eliminate all except the Platelet Factor 3. This fall in prothrombin activity was not associated with any clinical hemorrhagic tendency.

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Chapter 9

Studies of Blood Volume and Transfusion Therapy in the Korean Battle Casualty*

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During the years 1952–53 in the Korean War, there was a trend toward giving increasingly large amounts of blood throughout resuscitation. It was not unusual to administer to the critically injured soldier 15 to 30 pints of blood on the day of injury. Much of the blood was given after the control of obvious hemorrhage. The desirability of this practice was often questioned, but was based on the belief that adequate resuscitation (i. e., stabilization of blood pressure and pulse rate at relatively normal levels, subsidence of clinical symptoms and signs of shock) was principally a function of restoration of blood volume. Likewise, during and after surgery, maintenance of blood volume seemed to be the most critical factor in the recovery or death of the wounded patient. The present studies of blood volume in battle casualties were therefore undertaken in an effort to evaluate these clinical impressions by more objective, quantitative methods, particularly with reference to the desirability and necessity for massive transfusions. All blood used in the Korean Theater was either type O, banked blood or, rarely, fresh compatible blood.

Several previous studies relative to blood volume following wounding have been carried out.[1, 7, 10] In general, these investigations have stressed primarily the clinical status of the patient as correlated with his blood volume at the time he entered the hospital. For several reasons, we decided to place our emphasis principally on blood volume in the postoperative rather than the early *resuscitative phase* of the patient's course. (1) It was felt that more could be learned about the adequacy of transfusion and its effect in maintaining blood volume through resuscitation and surgery. In particular, determinations at this time would provide quantitative answers as to the

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necessity for large transfusions. (2) In most instances adequate hemostasis was achieved at this time allowing for adequate mixing of the labeled cells or dye without significant loss during mixing. (3) Likewise, the rapid administration of blood or colloids was not necessary here, so that mixing phenomena of labeled cells and dye could be observed without being confounded by concomitant mixing of other rapidly infusing fluids used for resuscitation.

Those patients, therefore, whose blood volumes were determined with labeled red cells, were studied during the first 12 to 48 hours after surgery. Where the dye T–1824 was used it was often necessary to wait until the day following surgery to avoid interfering effects due to elevated plasma hemoglobin.

Methods

Labeled Red Cell Method. Labeling of red cells was carried out using radioactive chromium as the tagging material. Chromium ^{51} was used in preference to P^{32} because of the more lasting incorporation of Cr^{51} in the red cells as compared to P^{32}. Since with the method used negligible escape of Cr^{51} from the red cells occurs within the first 24 hours, prolonged study of mixing could be carried out and serial volumes determined without the necessity of relabeling new cells. The following is the method used for labeling the red cells and calculating the blood volume.

(1) *Preparation of labeled red blood cells.*
  (a) Place 10 ml. of sterile, physiologic saline and 150 to 200 microcuries of radioactive chromium in a sterile, glass-stoppered flask.
  (b) Add 15 ml. of fresh heparinized "O" blood to the centrifuge flask.*
  (c) Place the flask in an incubator at 38° C. and allow to react for 1 hour, mixing gently every 10 minutes.
  (d) Wash the red cells three times with sterile saline.
  (e) Suspend the washed red cells in 2 volumes of saline and store at refrigerator temperature until ready for use.
  (f) If the cells are to be stored for several hours before use, resuspend in 2 volumes of plasma obtained from bank blood.

(2) *Red blood cell volume determination.*
  (a) Mix the labeled red cell suspension thoroughly and aspirate into a syringe of suitable volume.

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*Fresh labeled "O" cells were used in preference to the patient's cells so that a source of labeled cells would be readily available on short notice whenever needed.

(b) Place at least 2.5 ml. of labeled blood from the syringe into a tared volumetric flask as a standard and weigh. Make to volume with distilled water.

(c) Weigh the syringe containing the material to be injected together with the needle to be used for injection.

(d) Inject the remaining labeled blood intraveneously and weigh the syringe and needle immediately without rinsing.

(e) Collect blood samples 20 and 40 minutes after injection and as indicated thereafter until mixing is complete. In most cases, multiple samples were taken until the last two aliquots differed by less than 5 per cent.

(f) Carefully determine the hematocrit of each sample. At least three hematocrits were obtained on each patient.

(g) Pipette exactly 5 ml. of each whole blood sample into a counting test tube. Likewise, pipette duplicate 5 ml. samples of standard into counting tubes.

(h) Count all standards and samples in a well-type scintillation counter.*

(3) *Computations.*

The blood volume is calculated using the standard dilution formula $C_1V_1=C_2V_2$ or $V_2=\frac{C_1V_1}{C_2}$ where

C_1=cpm/ml. of injected material
V_1=volume of injected material
C_2=cpm/ml. of patient's blood
V_2=volume of patient's blood.

In this instance:

$$C_1=\frac{\text{cpm/ml. of diluted standard x volume to which standard was diluted}}{\text{Weight of labeled blood used as standard}}$$

V_1=Weight of syringe and needle before injections minus weight after injection.
C_2=cpm/ml. of patient's blood after adequate time for mixing of labeled cells has been allowed.
V_2=Resultant calculated blood volume.
TRCV=Hematocrit x Total Blood Volume.
Plasma Volume=Total Blood Volume minus TRCV.

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*Standard scintillation counting technics were used.

Dye Method. When the dye T–1824 was used for plasma and blood volume determination, the technic of Gregerson *et al.*[8, 9] was utilized wherein three plasma samples were taken at 13–15, 30 and 45–60 minute intervals. The dye concentration of each sample was measured and plotted against time. The curve so obtained was extrapolated linearly back to zero time to correct for dye loss during the mixing period. This value at zero time gave the theoretical concentration of dye that would have occurred in the plasma if uniform mixing had been effected at the instant of injection and none of the dye had been excreted. Where abnormal plasma hemoglobin levels or an interfering cloudiness were suspected the samples were discarded. Each reported determination was made on the basis of three valid samples with the exception of those so indicated where extrapolation was on the basis of only two. When only one plasma level was obtained or when a linear plot did not result, the observation was discarded. The total blood volume was calculated from the plasma volume and the hematocrit value. Where simultaneous blood volumes were determined using labeled cells and dye, the two were administered separately via different veins to avoid error through loss during changing of syringes.

In calculating the total blood volume from the plasma volume or red cell volume, no correction factors were used to offset the possible error introduced by differences between venous and total body hematocrit. The estimated normal blood volume used for the dye method was 8 per cent of body weight, and for the labeled red cell method 70 ml./kilo body weight.[2]

Controls

(1) *Radio chromium, red cell tag.*

(a) Fresh red cells labeled with Cr^{51} and resuspended in 2 volumes of saline showed a transfer of 1.5 per cent of the total radioactivity to the suspending medium in 36 hours. When bank blood plasma was used for resuspension less than 0.5 per cent of the total radioactivity appeared in the supernatant fluids.

(b) Counting of multiple samples of standard Cr^{51} solution, a total of 10,000 counts for each sample, gave a standard deviation of 1.6 per cent.

(c) The red cell volumes of several normal individuals were determined as indicated in Table 6. Three duplicate determinations done several days apart gave volumes differing by 0.5, 1.7 and 4.2 per cent of the total. In each instance the second determination was made with cells that had been stored 6 hours after labeling with Cr^{51}.

(2) *Evans Blue Dye.*

Nine patients who received no transfusions had multiple plasma volume determinations during their postoperative course. Using these volumes and the hematocrit to compute the red blood cell volume it was found that the results were constant within an estimated variation of S. D. = ± 5 per cent.

Results

The results are tabulated in Tables 1 through 3.

Careful evaluation of mixing was carried out during the first 60 to 90 minutes in all patients to make sure that the volume was calculated from completely mixed samples. Samples were taken until successive counts differed by less than 5 per cent. Furthermore, because it was suspected that relatively sequestered areas of blood might exist in some of these patients,[5, 13, 15] later samples were taken in nine individuals. It was reasoned that if such areas existed and they were not completely sequestered, late samples might have mixed into larger volumes which were not apparent in earlier samples. The results of these studies are seen in Table 2. It can be seen that even though the early samples had reached a plateau and agreed with one another within less than 5 per cent, later samples taken at varying intervals revealed slightly greater apparent volumes in most instances. In all but Case No. 1, the later samples also fell within less than 5 per cent of one another.

Table 1A. Blood Volume Determined with Radioactive Chromium

Abdominal Wounds

Case No.	Wt. (kg)	Hct.	TRCV		Pl. Vol.		Bl. Vol.		Blood Rec'd (ml.)	% Normal	Wounds
			ml./K	Tot.	ml./K	Tot.	ml./K	Tot.			
1		46		1, 912		2, 436		4, 346	2, 000		Carbine wounds—lac. of spleen and stomach.
2	74. 6	38	17. 4	1, 298	28. 6	2, 118	46. 0	3, 416	6, 000	65	Carbine wounds entering over left inguinal ligament, perf. bladder and leaving via left buttock. Retroperitoneal muscle damage.
3	72. 8	46	26. 4	1, 990	34. 8	2, 533	60. 2	4, 523	3, 000	89	Carbine wounds entering left flank. 5 perfs. of jejunum, 2 perfs. descending colon.
4	58. 6	36. 5	19. 6	1, 148	36. 4	2, 132	56. 0	3, 280	10, 500	80	Mortar—cpd. fracture rt. ilium with perf. wound of flank, buttock and rt. retroperitoneal area. Tremendous muscle destr. and hemorrhage.
	58. 6	38. 5	23. 8	1, 390	36. 2	2, 221	60. 0	3, 611	11, 500	86	1 day later.
5		48. 5		1, 780		2, 052		3, 832	6, 000		Mortar—extensive lac. rt. lobe of liver, perf. of ascending colon, duodenum, ileum; lac. 2 lumbar veins; perf. of diaphragm.
6	66*	42. 5	16. 4	1, 082	23. 6	1, 558	40. 0	2, 640	500	57	Mortar—6 perfs. of ileum, fracture mid-left ilium, muscle injury to gluteus, iliacus and psoas; 2,000 cc. blood in peritoneal cavity.
	66	43. 5	27. 5	1, 820	38. 5	2, 540	66. 0	4, 360	6, 000	94	1 day later—postoperatively.
7	63. 8	68	47. 1	3, 002	25. 5	1, 628	72. 6	4, 630	7, 000	104	Mortar—extensive lac. small bowel and colon, requiring resection of 2 segments. Renal insufficiency, purpura, death.
	63. 8	68	48. 7	3, 105	26. 0	1, 655	74. 5	4, 760	7, 000	107	1 day later.

*In shock.

Table 1A. Blood Volume Determined with Radioactive Chromium—Continued

Case No.	Wt. (kg)	Hct.	TRCV		Pl. Vol.		Bl. Vol.		Blood Rec'd (ml.)	% Normal	Wounds
			ml./K	Tot.	ml./K	Tot.	ml./K	Tot.			
						Abdominal Wounds					
	63. 8	48	29. 1	1, 855	34. 1	2, 175	63. 2	4, 030	7, 000	91	1 week later.
8	56. 4	48	28. 6	1, 615	33. 5	1, 885	62. 1	3, 500	2, 000	89	Mortar penetrating pelvis dorsally—perf. of ileum in 4 places, perf. of rectosigmoid.
$\overline{M}$	65. 4	45. 8	27. 1	1, 772	33. 3	2, 171	60. 4	3, 943	5, 300	86. 7	
						Extremity Wounds					
9		41		1, 625		2, 339		3, 964			Mortar—perf. rt. and left thighs, left elbow, CCF rt. patella with multiple bone fragments in knee.
10	60. 0	31. 0	16. 0	962	37. 4	2, 246	53. 4	3, 208	2, 500	76	Mortar—rt. inguinal region and rt. buttock with a large amount of muscle damage.
11	95. 5	43. 5	27. 1	2, 580	33. 0	3, 128	60. 1	5, 708	6, 500	85	Mult. pen. wds. both thighs. Cpd. comm. fracture of tibia and fibula bilaterally. Traumatic amput. of rt. hand.
12	72. 6	40. 0	19. 4	1, 410	31. 0	2, 250	50. 5	3, 660	3, 500	72	Mortar—CCF upper 1/3 rt. tibia. Large perf. wds. of rt. and left thighs.
13	72. 8	32. 0	13. 9	1, 010	31. 4	2, 290	45. 3	3, 300	4, 250	65	CCF of left tibia and fibula with extensive soft tissue damage.
14	61. 3	33. 0	16. 0	982	34. 6	2, 118	50. 6	3, 100	4, 500	73	CCF of rt. tibia and fibula. Perf. wound of thigh.

15	76. 5	32. 0	16. 8	1, 285	37. 8	2, 895	54. 6	4, 180	9, 500	78	Traumatic severance of femoral artery and vein in mid-thigh (rt.). Extensive muscle damage medial rt. thigh. Subtotal severance sciatic nerve.
$\overline{M}$	73. 1	36. 0	18. 2	1, 408	34. 2	2, 466	52. 4	3, 874	5, 125	75	
Abdominal—Extremity Wounds											
16	72. 8	51	33. 7	2, 452	32. 4	2, 356	66. 1	4, 805	1, 500	94	Mortar wounds—both legs. Small intrapelvic fragment at level of S_1. 5 perfs. of ileum.
17*		36. 0		1, 956		1, 814		2, 770	3, 500		Multiple mortar wounds both hands, arms and thighs. 30 perfs. of small bowel. Lac. left common iliac vein.
18	71. 0	43. 0	23. 5	1, 675	33. 5	2, 380	57. 0	4, 055	7, 500	82	Artillery wounds—Traumatic amput. both arms. Mult pen. wds. of liver. Multiple perfs. of small bowel.
19*	59. 6	40. 0	16. 7	992	26. 6	1, 589	43. 3	2, 581	7, 000	62	Mine injury—CCF left tibia and fibula. CCF rt. tibia and fibula lower third with traumatic amput. rt. foot: large perineal wound with retroperitoneal hematoma.
$\overline{M}$	67. 8	42. 5	24. 6	1, 769	30. 8	2, 034	55. 5	3, 553	4, 875	79	

*In shock.

Table 1A. Blood Volume Determined with Radioactive Chromium—Continued

Thoraco-Abdominal Wounds

Case No.	Wt. (kg)	Hct.	TRCV		Pl. Vol.		Bl. Vol.		Blood Rec'd (ml.)	% Normal	Wounds
			ml./K	Tot.	ml./K	Tot.	ml./K	Tot.			
20	67. 4	43. 0	26. 2	1, 760	37. 2	2, 513	63. 4	4, 273	0	91	Mortar wds. thru 10 I. S., mid axillary line of left chest, perforating diaphragm and left lobe of liver. Fragment embedded in serosa hepatic flexure.
21	54. 0	57. 0	45. 5	2, 480	37. 9	2, 055	83. 4	4, 535	7, 000	120	Mortar wds.—Pen. avulsive thoraco-abdominal wound, left with fracture of ribs 9 and 10, hemothorax; laceration of diaphragm, spleen and stomach.
	54. 0	50. 7	42. 9	2, 320	45. 7	2, 470	88. 6	4, 790	7, 000	127	3 days later.
	54. 0	41. 0	28. 1	1, 518	46. 7	2, 525	74. 8	4, 042	7, 000	107	9 days later.
22	52. 2	51. 0	41. 6	2, 170	43. 3	2, 260	84. 9	4, 430	1, 500	121	Mortar wds.—Fract. ribs 11 and 12, lac. of diaphragm, ruptured spleen, hemopneumothorax.
23	57	35	23. 5	1, 340	43. 7	2, 490	67. 2	3, 830	2, 500	96	Mortar wds.—SFW pen. rt. shoulder and entering chest. Hemothorax. Pen. wound rt. lobe of liver.
	57	37	28. 4	1, 617	48. 3	2, 753	76. 8	4, 370	3, 100	110	2 hours later—after 600 blood with Hct. 46.
$\overline{M}$	57. 6	46. 5	34. 2	1, 937	40. 5	2, 329	74. 7	4, 267	2, 500	107	

Chest-Extremity Wounds											
24*	82. 0	28	9. 0	736	24. 4	2, 004	33. 4	2, 740	10, 000	48	Mortar wounds—Mult. Pen. wds. rt. chest, hemothorax. Mult. fragments in both thighs. Fractures of left radius, upper third left tibia, 4 and 5 metacarpals left hand.
25	68. 0	42	28. 2	1, 915	39. 8	2, 835	68. 0	4, 750	10, 000	100	Mortar wds.—Fracture of pelvis, rt. humerus compound, comm. Hemopneumothorax.
26	79. 5	43	23. 8	1, 890	33. 7	2, 290	53. 0	3, 600	7, 500	65	Mortar wds.—Perf. SFW neck and chest. Massive hemopneumothorax. Extensive lac. upper lobe left lung.
$\overline{M}$	76. 5	37. 6	20. 3	1, 513	32. 6	2, 376	51. 4	3, 696	9, 166	71	
Miscellaneous Wounds											
27*	50. 0	43. 0	28. 3	1, 445	39. 0	1, 915	67. 3	3, 360	4, 500	96	Mortar wds.—Right temporal wound with intracranial shell fragments and bone fragments. Severe CCF of mandible with extensive hemorrhage. CCF left humerus. SFW left knee.
28	75. 0	40. 0	16. 4	1, 230	26. 4	1, 980	42. 8	3, 210	8, 500	61	Artillery wd.—CCF left temporoparietal area of skull with depression. CCF rt. femur. Compound fracture rt. radius and ulna.
$\overline{M}$	62. 5	41. 5	22. 3	1, 337	65. 4	1, 947	55. 0	3, 285	6, 500	79	

*In shock.

Note. 1. The preoperative volumes of Case No. 6 are not included in the mean for the group.
2. Only the initial postoperative volume of Case No. 7 is included in the mean for the group.

Table 1B. Blood Volume Determined with T-1824

Abdominal Wounds

Case No.	Date Injured	Wt. (kg)	Hct.	TRCV (ml.)	Pl. Vol. (ml.)	Blood Vol. (ml.)	Blood Rec'd (ml.)	% Normal	Date of Vol.	Est. Normal (ml.)	Wounds
29	9 Jun	56. 2	47	2, 150	2, 420	4, 520	5, 500	101	10 Jun	4, 500	SFW—Face, neck, eye, perf. stomach, small bowel, middle colic artery.
			48	2, 050	2, 400	4, 450	0		16 Jun		
30	14 Jul	83. 8	40	1, 670	2, 720	4, 390	6, 500	66	15 Jul	6, 700	Mortar wds.—Pen. wound of flank, multiple perf. of small bowel and colon, perf. of ureter, retroperit. hematoma.
			39	1, 860	3, 160	5, 020	0		17 Jul		
			46	2, 340	2, 910	5, 250	1, 000		20 Jul		
31	28 Jul		46	2, 740	3, 490	6, 230	10, 500		28 Jul		Carbine wds.—Perf. of duodenum and I. V. C. Post-traum. renal insufficiency.
			47	2, 780	3, 400	6, 180	1, 000		29 Jul		
32	2 Sep	77. 6	49	2, 170	2, 450	4, 620	7, 500	75	5 Sep	6, 200	Machine gun—Perf. of internal iliac, arter., vein and colon.
			41	2, 040	3, 190	5, 232	0		9 Sep		
			45. 5				7, 500	80. 6			
Extremity Wounds											
33	6 Jun		44	1, 780	2, 260	4, 040	4, 500		7 Jun		Perf. fem. art. and vein, pen. wds. both lower extremities, transfus. react. 14 Jun c̄ dev. of oliguria. Blood +.

34	15 Jun	65. 0	35	1, 230	2, 380	3, 610	7, 000	68	16 Jun	5, 200	Mortar wds.—Massive muscle wd. of thigh c̄ cp'd commin. fract. of pelvis. Two perf. of fem. and iliac ar. Died 16 June.
35	7 Jul	61. 2	33	1, 010	2, 190	3, 140	4, 000	64	8 Jul	4, 900	Mine injury—Came in in shock. Traumatic amp. of left foot, macer. and fractures rt. foot.
			25	940	2, 980	3, 920	0		10 Jul		
36	7 Jul	77. 6	37	1, 800	3, 200	5, 000	7, 500	81	8 Jul	6, 200	Mine wd.—Traumatic amp. of rt. foot. Destruction of muscle of calf.
			33	1, 850	3, 900	5, 750	0		10 Jul		
37	18 Jul	61. 3	36	1, 400	2, 720	4, 120	8, 500	84	18 Jul	4, 900	Mine injury—Traumatic amp. left foot. Muscle destruction rt. calf.
			28	1, 360	3, 640	5, 000	0		21 Jul		
			35	1, 650	3, 200	4, 850	1, 500		25 Jul		
38	18 Jul		34	1, 240	2, 630	3, 870	3, 000		19 Jul		Mine injury—Traumatic amp. both legs at calf.
			33	1, 540	3, 260	4, 800	1, 000		21 Jul		
			42	2, 200	3, 300	5, 500	1, 500		25 Jul		
39	12 Aug		40	1, 930	3, 010	4, 940	8, 000		13 Aug		Mine injury—In shock on entry. Extens. cp'd. commin. fract. both tibia c̄ traumat. amp. left leg at calf. Rt. leg at calf incompletely amp. Massive wd. left arm and of muscle and skin of thighs. Gas gangrene. Renal insuff.
40	19 Aug	70. 0	26	770	2, 380	3, 150	9, 500	56	19 Aug	3, 600	Artillery wds.—Massive cp'd. commin. fract. both femurs and pelvis. Massive muscle destruction.
			24	1, 010	3, 200	4, 210	500		20 Aug		
			52	2, 700	2, 700	5, 400	5, 000		23 Aug		

Table 1B. Blood Volume Determined with T–1824—Continued

Abdominal Wounds

Case No.	Date Injured	Wt. (kg)	Hct.	TRCV (ml.)	Pl. Vol. (ml.)	Blood Vol. (ml.)	Blood Rec'd (ml.)	% Normal	Date of Vol.	Est. Normal (ml.)	Wounds
41	2 Sep	77. 6	41	1, 920	3, 100	5, 080	10, 500	82	2 Sep	6, 200	Mine injury—Traumatic amp. both legs, high thigh.
			44	2, 270	3, 140	5, 410	1, 500		6 Sep		
			47	2, 670	3, 260	5, 930	0		10 Sep		
42	6 Sep	77. 6	42	1, 690	2, 570	4, 260	7, 000	69	6 Sep	6, 200	Mortar wds.—Traumatic amp. left leg (high calf) and rt. foot. Soft tissue wds. rt. leg.
			47	1, 600	1, 900	3, 500	0		7 Sep		
			30	1, 480	3, 060	4, 540	0		10 Sep		
43	20 Sep		38	600	1, 070	1, 870	12, 000		21 Sep		Mortar wds.—All four extremities amputated. Both legs at calf and both hands.
			47	1, 665	1, 880	4, 180	11, 500		22 Sep		
44	22 Sep	70. 0	38	1, 360	2, 420	3, 780	6, 000	67	23 Sep	5, 600	Artillery wds.—Traumatic amp. of rt. leg at knee, comp. commin. fracture left radius and ulna.
			37	1, 320	2, 440	3, 720	0		24 Sep		
			37. 0				7, 290	71. 4			

Abdomen+Extremity Wounds

45	4 Aug	77. 6	42	1, 270	1, 750	3, 020	10, 500	49	4 Aug	6, 200	Perf. of TVC., small bowel, poplit. artery. In prof. shock.
			45	1, 650	2, 010	3, 660	1, 500		7 Aug		
			41	1, 410	2, 170	3, 580	1, 000		12 Aug		

Thoraco+Abdominal Wounds

46			63	2, 500	1, 630	4, 130	6, 000		4 Sep		Carbine wds.—Perf. of lung, liver, stomach and diaphragm and colon.
			51	2, 760	2, 870	5, 630	0		6 Sep		
			47	2, 870	3, 520	6, 380	0		15 Sep		

Thorax+Extremity Wounds

47	12 Jun	68. 8	38	1, 350	2, 280	3, 630	16, 500	66	12 Jun	5, 500	Carbine wds.—Perf. lung, rt. axill. vein and art., med. and ulnar nerve.
			38	1, 740	2, 900	4, 640	1, 000		14 Jun		
			42	1, 980	2, 750	4, 730	500		17 Jun		
48	11 Jul	83. 8	40	2, 180	3, 450	5, 730	3, 000	85	15 Jul	6, 700	Mine injury—Perf. lung, arm, brachial plexus, cp'd. fract. clavicle, small wd. of face.
			39				9, 750	75. 5			

Table 1B. Blood Volume Determined with T-1824—Continued

Miscellaneous Wounds

Case No.	Date Injured	Wt. (kg)	Hct.	TRCV (ml.)	Pl. Vol. (ml.)	Blood Vol. (ml.)	Blood Rec'd (ml.)	% Normal	Date of Vol.	Est. Normal (ml.)	Wounds
49	1 Jul	80. 0	36	1, 970	3, 650	5, 620	4, 000	88	2 Jul	6, 400	Mortar wd.—Perf. of lung, arm, massive wound of liver.
			32	1, 800	4, 000	5, 800	0		14 Jul		
			33	1, 360	3, 020	4, 380	0		7 Aug		
50	2 Jul		63	4, 080	2, 650	6, 730	6, 000		2 Jul		Mortar wds.—Cp'd. comm. wd. of mandible c̄ destruct. of jaw. Massive hemorrhage. Devel. pulm. edema. Admitted in shock.
51	4 Aug.	80. 0	52	2, 270	2, 080	4, 350	2, 000	69	4 Au	6, 400	S. Frag.—Perf. lung, diaphr. and liver. Massive wd. of liver; small wds. of lower extrem. and arm.
			45	2, 100	2, 600	4, 700	0		7 Aug		
52	26 Aug	70. 5	46	2, 390	2, 920	5, 210		93	26 Aug	5, 600	S. F.—Perf. of heart c̄ peric. tamponade. Perf. of lung. Fract. 4 ribs. Perf. diaphr., stomach, small bowel, colon, spleen, left kidney. Cp'd. comm. fract. left humerus, tibia.
53	20 Sep	53. 8	44	1, 420	1, 960	3, 380	16, 000	72	21 Sep	4, 700	Mortar wds.—Multiple wds. of small bowel, perf. of colon, liver and lung and fem. artery. Traumat. amp. left calf at knee. Traumat. small soft tissue wds.
			40	1, 680	2, 510	4, 180	1, 500		22 Sep		
			48				7, 000	80. 5			

Table 2. Blood Volume as Related to Time of Sampling

Case No.	Early Samples		Late Samples		Diff.
	Time Interval (Min.)	Volume (ml.)	Time Interval (Hrs.)	Volume (ml.)	
4	20, 40	3, 280	1, 2	3, 660	380
9	15, 30, 45	3, 960	22	4, 064	104
10	20, 40, 60	3, 208	6, 14¾, 28	4, 773	1, 565
12	20, 40	3, 660	1, 2½	3, 660	0
18	20, 40	3, 835	1, 5	4, 055	220
21	40, 60	4, 790	1¾	4, 790	0
25	30, 60	4, 400	4½, 5½	4, 775	375
28	No early samples		1, 2, 5	3, 210	
17	20, 40, 60	2, 770	3	3, 373	603

The interpretation of these findings is open to some question owing to the possibility of selective destruction of labeled cells. Two patients were given hexamethonium after the early mixing of labeled cells was complete. It was felt that if slowly mixing, stagnant areas of blood existed, the opening of arterioles and increased flow caused by hexamethonium might improve the circulation through such sites with more complete mixing of labeled cells therein. This process, if it occurred, would increase the measured blood volume. In the two instances, sufficient drug was administered to lower the systolic pressure from the range of 120 to 130 down to 90 to 100. Neither individual showed any increase in volume at intervals of 30 to 60 minutes thereafter.

The postoperative blood volume measurements revealed one outstanding result: namely, that large transfusions were a definite necessity in many of these patients and very rarely resulted in over-transfusion. In fact, regardless of the amount of blood received, the vast majority of patients emerged from surgery with some deficit of total blood volume. Of the 25 patients studied with dye none revealed an initial postoperative blood volume greater than normal. In only 3 patients, out of 28 studied with Cr^{51} labeled red cells, was over-transfusion present, and in none of these was there any evidence of cardio-respiratory difficulty. This was probably due to the fact that the degree of over-transfusion was minimal. Two of the three over-transfused patients were followed with successive blood volume measurements. In one instance, the red cell volume returned to normal in 9 days and in the other in 7 days. The latter's course, however, was complicated by jaundice and purpura apparently due to thrombocytopenia. Of the three over-transfused patients, one had an abdominal wound and the other two had thoraco-abdominal wounds. They received 7,000, 7,000 and 1,500 ml. of blood, respectively.

Clinical State

In general, varying degrees of hypovolemia were tolerated very well by the group during this postoperative period. Fourteen or 58 per cent of the weighed patients studied with labeled cells showed deficiencies of 15 per cent or more of the average normal for their weight. We would class this group as definitely under-transfused. The average deficiency for these patients was 32 per cent. However, of the 14 patients only 3 were in shock, these patients showing deficiencies of 38, 43 and 52 per cent, respectively. The others were doing well postoperatively with no clinical evidence of shock. The average amount of blood which had been received prior to the blood volume determination in this hypovolemic group was 6,740 ml. This figure is in contrast to the group whose deficit was less than 15 per cent. Their average replacement was 3,187 ml. or less than half that of the hypovolemic patients.

The results were even more striking in the patients studied with dye. Fourteen of the eighteen patients whose weights were known and whose normal blood volume could therefore be calculated revealed a deficit of greater than 15 per cent. Their average deficit was 31 per cent. All these patients were doing well postoperatively with no clinical evidence of shock. Their blood requirement pattern was similar to those studied with labeled cells, the group with greater than 15 per cent deficit having received 7,785 ml. and the group with less than 15 per cent deficit receiving 4,160 ml. Thus those individuals who had required the most blood remained the most hypovolemic following surgery. It was in this group that the most massive transfusions were required.

In only one patient did shock exist in the presence of a normal blood volume. This patient had received severe head injuries, with shell and bone fragments in the brain substance. In addition, there were severe facial injuries and a compound comminuted fracture of the left humerus. This patient had received 4,500 ml. of blood prior to the blood volume determination, which measured 96 per cent of normal for his weight. The volume was done 3 hours before his death at which time his pulse was 140–160, respiration 40–50, B.P. 120/100 dropping to 90/70 during the succeeding hour. He died in severe pulmonary edema. The severe brain injury was undoubtedly of paramount importance here and may well explain the shock picture in the presence of a normal blood volume.

When the patients are placed in categories dependent upon the location of their wounds, several trends relative to blood volume and blood requirements come to light. In view of the relatively small numbers of patients, these trends must be considered tentative. They seem to be dependent primarily on one fundamental factor, the presence or absence of large areas of muscle injury. In the extremity wounds where a large amount of muscle injury was almost invariably present, large amounts of blood were necessary during resuscitation and surgery. Yet when the blood volume was determined postoperatively by either method, all members of the group fell in the hypovolemic class with deficits in volume of 15 per cent or more and an average hematocrit of 36.5. On the other hand, those who had abdominal wounds, though they had received a similar amount of blood compared to those with extremity wounds, revealed postoperative blood volumes more closely approximating normal and an average hematocrit of 45.8. The excess loss of blood from wound of muscle is easily understood when one considers the local pathology involved in wounds caused by implements of war. Although there may be only a small wound of entrance, there is a large amount of destruction of the underlying muscle. This is particularly true in high-velocity missile wounds. Bleeding from the large mass of damaged muscle continues from the time of injury until operation. During this time, the blood loss is greater than the observer generally realizes. The importance of other factors, such as hemolysis and trapping of blood, as added mechanisms for the causation of these low blood volumes is not fully known at the present time

Relation of Hematocrit

Table 3 illustrates 10 patients with extremity wounds on whom serial postoperative hematocrits were done. They show a consistent fall in hematocrit. One factor which may contribute in part to this effect is the rise in plasma volume observed in many hypovolemic convalescent patients. A rising plasma volume and falling hematocrit was noted in the absence of any significant change in the total red cell volume indicating a dilution effect as being at least partially responsible for the falling hematocrit.

Table 3. Hematocrit Changes During Resuscitation, Operation and Convalescence

Patient No.	Hematocrit							
	Admission	Postoperative	Days Postoperative					
			1	2	3	4	5	6
		Abdominal Injuries						
1	32	52	38	39	39	40		
2	44	42	47	40				
3	40	------	64	62				
4	50	61	66	------	65			
5	43	45	50	55	48	47		
6	63 (albumin*)	52 (albumin*)	42	41	47	45	45	
7	34	51	44	40	43	45	45	49
8	48	------	46	------	49	43	40	39
9	------	59	52	49	45	45	43	44
10	41	43	57					
		Extremity Injuries						
1	40	43	34	------	23			
2	------	41	41	39	36			
3	------	42	44	38	33			
4	36	35	35	34	29	32		
5	36	44	43	36	31	32		
6	------	47	44	37	39	32		
7	41	38 (blood*)	47	42	40	36	35	
8	42	44	38	37	36	36		
9	37	35	32	31	33	33		
10	36	35	35	34	29	------	----	22

*Intravenous therapy.

As has been previously reported, hemoconcentration characteristically follows severe intra-abdominal injuries.[1] This is probably due to the loss of plasma in excess of red cells into the bowel wall, mesentery and peritoneal cavity. Serial postoperative hematocrits in patients with abdominal injuries as compared with the postoperative changes following wounds of the extremities, are seen in Table 3. Because hemoconcentration and plasma loss were so frequently remarked, surgeons often administered dextran as an adjunct to blood transfusion therapy during and after repair of major intra-abdominal injuries. This was true during much of the current observation.

Comparative Blood Volumes

In 15 patients, simultaneous blood volume determinations were carried out using labeled red cells and T–1824. The results are recorded in Table 4. In general the methods agreed fairly well, the average difference being 16.3 per cent and falling in the range of difference found by previous investigators in normal individuals. In three patients (20 per cent), however, the discrepancy was considerably larger (26 to 39 per cent), the dye volume being larger in all instances. All three of these individuals had severe abdominal wounds, two of the three having lacerations involving the liver. This would suggest that the same factor causing hemoconcentration in such patients allows for leakage of dye out of the vascular system with resultant falsely high plasma and blood volume determinations. Peters[12] has commented previously on the loss of the dye, T–1824, from the blood stream particularly in the liver vasculature. The involvement of the liver in two of these three cases is therefore of added interest and significance. These data suggest that under certain circumstances the dye method may not be a reliable one.

Table 4. Comparison of Simultaneous Blood Volumes Determined With Chromium-Labeled Red Cells and T–1824

Case No.	Cr^{51} (ml.)	Dye (ml.)	Diff. (ml.)	Diagnosis	% Diff.
3	4,523	4,100	−423	(See Table 1)	9.8
4	3,280	4,580	+1,300		33.1
	3,611	4,920	+1,309		30.5
5	3,832	5,700	+1,868		39.1
9	3,964	3,490	−470		12.8
10	3,208	3,995	+787		19.7
12	3,660	4,150	+490		12.6
16	4,808	5,080	+272		5.5
18	4,055	3,940	−115		2.8
19	2,581	2,680	+99		3.8
20	4,273	5,600	+1,327		26.8
21	4,535	5,540	+1,005		20.2
	4,790	5,050	+260		5.3
22	4,430	4,470	+40		.8
*29	4,071	3,860	−211		5.1

*This patient tested preoperatively, therefore not included in Table 1A.

Discussion

The impression was originally gained by those in the North African-Mediterranean Theater[1] that blood loss rather than any other factor was responsible for shock in the wounded patient. Their findings indicated that the presence or absence of shock as well as its degree upon admission to the hospital was directly correlated with the deficiency in blood volume present at that time. The present studies lend support to these findings and extend the concept to the surgical and postoperative period where it is seen that tremendous amounts of blood are often necessary to maintain the blood volume close to normal range. Of the 52 patients studied, 31 or 59.6 per cent required over 10 pints of blood. In other words, over half of the patients studied required complete replacement of their blood volume. Of these 31 patients, 9 required 20 pints or roughly twice their blood volume. This group emphasized well the real necessity in some patients for massive transfusions. The average deficiency of blood volume in these 31 individuals after receiving such massive transfusion was still 25.2 per cent.

In addition to the problem of how large a circulating blood volume was necessary for these patients, was that of how effectively the blood transfused had increased that volume. Possibly present in almost every patient observed but becoming more apparent with the larger volumes of transfusion, was an apparent discrepancy between the amount of blood transfused and that actually measured after operation. This volume deficit appears to consist of both plasma and red blood cells. As examples the data of Table 5 were extracted from Table 1 and arbitrary estimates of admission blood volume made. Most of these patients were chosen as examples because the volumes involved were large enough to make errors in estimation of initial volume relatively insignificant. They demonstrate an average deficit of 5,373 ml. with a range from 1,600 to 7,900 ml. Likewise 10 patients requiring postoperative transfusions were studied with one or more determinations of their plasma volume with Evans Blue for up to 7 days after wounding. The results are tabulated in Table 7. When a transfusion intervened, between two determinations the change in circulatory red cells measured was significantly less than that expected in 6 of 12 instances. None of these patients showed clinical reason to suspect red cell loss.

Table 5. Showing Discrepancy Between Blood Received and Blood Volume Thereafter

(a) Pt. No.	(b) Wt. (Kg.)	(c) Estimated B. V. on Admiss. (ml.)[1]	(d) Vol. Transfused (ml.)[2]	(e) Postop. B. V. (ml.)[3]	(f) Deficit (ml.)[4]	(g) Remarks
30	84	2, 700	6, 500	[5] 4, 400	4, 800	Abd. wound
32	78	2, 500	7, 500	[5] 4, 600	5, 400	Abd. wound
34	65	2, 100	7, 000	[5] 3, 600	5, 500	Ext. wound
37	61	2, 000	8, 500	[5] 4, 100	6, 400	Ext. wound
38		2, 500	3, 000	[5] 3, 900	1, 600	See note [7]
41	78	2, 500	10, 500	[5] 5, 100	7, 900	See note [7]
5		2, 500	6, 000	[6] 3, 800	4, 700	Abd. wound
11	96	3, 000	6, 500	[6] 5, 700	3, 800	Ext. wound
15	76	2, 500	9, 500	[6] 4, 200	7, 800	Ext. wound

[1] Estimated as 40% of normal.

[2] Volume of whole blood received during resuscitation and operation.

[3] The circulating blood volume measured several hours to 1 day after operation.

[4] Columns (c) and (d) less column (e).

[5] Measured with Evans Blue and hematocrit.

[6] Measured with Cr^{51} and hematocrit.

[7] These patients entered with tourniquets in place above traumatic amputations and underwent uneventful amputations with minimal blood loss and had thereafter only the clean amputation wounds.

Table 6. Red Cell Volumes as Determined With Radio-Chromium

Normal Subjects

(a) Date	(b) Subj.	(c) Wt. (Kg.)	(d) Hct. (%)[1]	(e) RBCV. Predicted Normal (ml.)[2]	(f) RBCV. Measured (ml.)[3]
2 Dec.	A	51	42	1, 600	[4] 1, 780
6 Dec.			40		1, 750
4 Dec.	B	89	45	2, 750	1, 900
11 Dec.			40		1, 820
7 Dec.	C	65	44	2, 000	2, 560
9 Dec.	D	71	44	2, 200	1, 860
13 Dec.			45		1, 870
11 Dec.	E		46		2, 180

[1] Hematocrit determined on the specimens taken for Cr^{51} determination.

[2] Red blood cell volume expected on the basis of 30 ml./Kg. body weight.

[3] Red blood cell volume measured.

[4] Female.

Table 7. Red Blood Cell Volume Response to Transfusion, Measured With Evans Blue

(a) Case No.	(b) RBC Rec'd (ml.)[1]	(c) ΔRBC Observed (ml.)[2]	(d) ΔRBC-RBC Rec'd. (ml.)[3]	(e) % of RBCV [4]	(f) % of RBC Rec'd.[5]
Fresh Blood Received					
47	450	+390	−60	4.0	−13
	225	+240	+15	0.8	+6
30	450	+480	+30	1.7	+6
37	675	+290	−385	28	−58
38	450	+300	−150	10.8	−33
	675	+660	+15	0.8	−2
40	2250	+1710	−540	36.0	−23
41	675	+350	−325	16.0	−48
Bank Blood Received					
31	450	+210	−240	3.9	−53
40	225	+230	+5	0.5	+2
53	675	+260	−415	37	−62
43	675	+1065	+390	35	+58

[1] Red cells received by transfusions between measurements of the plasma volume.

[2] The change in red cell volume as measured by plasma volume and hematocrit determinations before and after transfusion.

[3] The difference between columns (a) and (c).

[4] Column (d) expressed as per cent of the total measured red cell volume.

[5] Column (d) expressed as per cent of the transfused red cell volume.

It was because of these consistently low blood volumes after large transfusion and the discrepancy between the volume of blood infused and that measured thereafter that such concern was shown over the possibility of incomplete mixing of labeled cells in relatively sequestered areas of blood volume. If large amounts of blood were pooled in areas relatively inaccessible to mixing, falsely low total blood volumes would be the result. Although the blood volumes calculated from late samples were slightly greater than those calculated from early ones, in no instance did they result in a blood volume of 5,000 ml. or over. One of the ten patients showed an increase of 1,565 ml. in blood volume as calculated from the late samples. He had previously been resuscitated with only 2,500 ml. of blood. Of the remaining patients, seven received 10,500, 10,000, 8,500, 7,500, 7,000, 3,500 and 3,500 ml. respectively, and the blood volume increase when calculated from the late samples as compared with the early samples was 600 ml. or less in every instance. Likewise in the two patients given hexamethonium no increase in blood volume occurred concomitant with the fall in blood pressure. Furthermore, in those patients who had received massive transfusion and survived, none developed clinical or laboratory evidence of over-transfusion during their postoperative course. If such a pooling mechanism as has been postulated existed early, one would expect a reversal of this process during clinical recovery with mobilization of substantial amounts of trapped blood and some resultant evidence of over-transfusion. In no instance did such occur. Although these data are not sufficient for positive conclusions, they do not support the concept that a significant amount of pooling existed in these patients receiving massive transfusions.

Further answers to this question might be obtained by two approaches. (1) Weigh the patient on an accurate scale when he enters the hospital. When resuscitation and surgery are completed, weigh again and determine the blood volume. Where such large volumes of infused blood are involved, one should see significant gains in weight if most of the blood has been retained; little or no change if it is being lost externally as fast as it is being infused. Correlating the postoperative blood volume with change in weight would thus help clarify the question of loss versus pooling. Obviously if most of the bleeding was into the tissues little would be learned by this procedure. (2) Determine the blood volume postoperatively with chromium labeled cells. Determine the hemoglobin to Cr^{51} ratio in blood and in tissue biopsies such as muscle. If large amounts of blood are sequestered in the tissue and inaccessible to the labeled cells, the hemoglobin to chromium ratio will be increased considerably in the tissue.

The quality of bank blood used for transfusion was investigated [3] and so far as indicated by the indices used (plasma hemoglobin, plasma potassium and osmotic fragility) this blood was comparable to that available in the United States.

Investigations by means of the Ashby count, as reported previously,[3] indicate that in a small portion of A, B and AB recipients receiving large amounts of O blood there will be a destruction of the patient's own cells extending over several days but this is relatively infrequent and usually involves volume changes much smaller than those reported here.

The relative importance of hemolysis of recipient and donor cells as a contributing cause for the large requirement of blood replacement in these patients is not fully known at the present time. These patients do not show overt clinical manifestations of rapid blood destruction such as chills, fever, jaundice, etc. Moreover, the average plasma Hg done immediately after surgery in 22 patients who had received an average of 12 pints of blood each day was only 18 mg. per 100 ml.[3] (normal 5 mg. per 100 ml.). Since the intravenous infusion of 10 to 16 gm. of hemoglobin (equivalent to hemolysis of 60 to 100 ml. of blood) in normal individuals will induce plasma Hg levels of greater than 300 mg. per 100 ml.,[6, 11] the levels found in these postoperative patients would be indicative of minimal intravascular hemolysis. The rate of plasma hemoglobin clearance is of course a factor here. The most rapid clearance rate found in the group studied was 5 mg. per 100 ml. per hour, which would be insufficient to lower a significantly high concentration of hemoglobin to the levels found even over a period of many hours. Likewise the observed bilirubin levels in a similar group of patients [14] would correspond to a relatively small degree of blood destruction.

The rate of plasma clearance, principally by the liver, is again a critical factor here and the necessary data for such evaluation in these patients are not at hand. The infusion of 16.4 gm. of hemoglobin [6] (equivalent to hemolysis of approximately 100 ml. blood) in a normal individual resulted in a plasma bilirubin concentration of 1.4 mg. per 100 ml. 10 hours later, with a gradual fall thereafter and remaining greater than the pre-injection level 24 hours later. Clearance of bilirubin in the wounded patient, where impaired hepatic function has been shown by others [1, 14] would be expected to be slower than in normals. Therefore the 6-hour postoperative average level of 2.5 mg. per 100 ml. which is the highest level reached in any of the preoperative and postoperative specimens would imply relatively small amounts of hemolysis.

The postoperative hematocrit afforded a relatively poor index to the requirements for transfusion. Because of rapid changes in plasma volume which take place independently from changes in red cell volume after extensive blood loss, the hematocrit gives little information about the actual red cell volume at any given time. By the same token, any conclusions concerning the status of total blood volume drawn from hematocrit data alone are likely to be in error.

Conclusions

Blood volume determinations have been carried out postoperatively in 52 wounded patients. These patients required large amounts of blood to maintain them through the phases of resuscitation and surgery. Generally those with extremity wounds, where large amounts of muscle destruction had taken place, required the largest amounts of blood and still remained the most hypovolemic following surgery. However, no matter where the injury was located, if considerable areas of muscle were involved, large amounts of blood were usually required.

Over-transfusion occurred in only three instances and in no case was it of sufficient degree to cause cardio-respiratory symptoms. The error in most cases was under-transfusion rather than over-transfusion.

Hematocrit determinations in the postoperative period are not a reliable index to the requirement for blood.

Where simultaneous blood volumes were determined with labeled cells and dye, the difference between the two was 16 per cent, the dye volume being greater in all but four instances. However, in severe abdominal wounds, especially with liver involvement, the discrepancy was much larger. Here the dye volumes were greater by 26.8, 33 and 39 per cent. This probably represents increased capillary permeability and gross vascular damage in the involved area with resultant leakage of dye.

The discrepancies between the large amounts of blood given and the small blood volumes determined thereafter are explainable on three possible bases: (1) Trapping of large amounts of blood in a sequestered state which mixes slowly or not at all. (2) Hemolysis of large amounts of donor and/or recipient erythrocytes. (3) Continued loss of blood either externally or into the tissues during the preoperative, operative and postoperative periods. The latter is believed, at the present time, to be the most important of these factors.

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Chapter 10

In Vitro Studies of Whole Blood During Shipment and Storage

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This study was designed for the following purposes:

1. To describe the changes of plasma hemoglobin, plasma potassium, whole blood glucose, and red cell osmotic fragility in bank blood collected and transported through the regular blood program channels.
2. To compare the in vitro quality of whole blood at varying periods of time following collection.
3. To compare whole blood collected, shipped and stored in bottles, and that in plastic bags.

Materials and Methods

This study was undertaken as a cooperative effort between personnel of the Department of Chemistry, 406th Medical General Laboratory, in Japan, and the Surgical Research Team in Korea.

Blood samples for examination of bottled blood were selected at random from stocks shipped from the United States. Collection of blood in plastic bags was done at the Blood Processing Laboratory, Travis Air Force Base, California, and these bags were shipped simultaneously with the regular quotas of bottled blood. For control studies of the effect of handling of blood for long shipments, collections of blood were made by the Blood Bank Laboratory Detachment, 406th Medical General Laboratory. All bloods were stored at a temperature of 2° to 6° C until examined and were transported through normal blood shipment channels.

Comparative studies of plasma hemoglobin, potassium and red cell osmotic fragility are reported herein. A series of whole blood glucose levels on preliminary shipments of blood is not recorded since it was found during the study that anticoagulant solutions of both NIH formula A and B were used in making collections. It was not possible to determine the ACD solution used in any instance. Only in the study of bottled blood and plastic bags, received as one shipment, are the glucose values reported.

Sampling

Bottles of blood were selected at random from stocks received and maintained by the local blood bank. Blood selected was that which would normally have been dispensed to the surgeon. The bottles were mixed by rolling from side to side for a period of 5 minutes. Bags were mixed by inversion for a similar period. Shaking was avoided. The selected unit of blood was sampled using a dry syringe and size 17 needle. Plasma samples for the studies were separated from the cells as soon as possible after collection.

Plasma potassium was determined by flame photometry using lithium as an internal standard. For convenience, the analyses done in Korea were on plasma samples stored under refrigeration for 3 or 4 weeks after they were drawn from the bottle of blood. Control studies demonstrated no change in potassium concentration during storage.

Plasma hemoglobin was determined by the method of Bing and Baker as modified at the 406th Medical General Laboratory.

Into a suitable clorimeter cuvette 0.6 ml. of 2 per cent benzidine base in glacial acetic acid, 0.2 ml. of suitably diluted plasma sample, and 0.2 ml. of 0.6 per cent hydrogen peroxide were placed in sequence named. After 1 hour 6 ml. of 20 per cent acetic acid was added and the transmission compared at wave length 640 mμ to standards of 5.0, 7.5 and 10.0 mg. per 100 ml. hemoglobin which were prepared by diluting whole blood. The unknown was diluted with normal saline to approximate the range of the standards. A Coleman Junior Spectrophotometer was used for these studies.

Red cell osmotic fragility was determined in phosphate-buffered saline solutions as described by Parpart *et al.*[1] Reagents for this examination were prepared as a single lot at the 406th Medical General Laboratory and used by both laboratories. A special shipment of Cutter and Fenwal plastic bags required preparation of a second lot of reagents.

Whole blood hematocrit was used to evaluate mixing of the blood samples. In any instances where the hematocrit varied by more than 5 per cent from day to day samplings, the determination was invalidated. Culture for bacteria was used to check the continued sterility of samples. Any bags or bottles which were found to be contaminated were eliminated from the study. One bag and two bottles were eliminated for this reason.

Results

The study was divided into three phases which are reported as follows:

1. Comparison in Japan and Korea of bank blood collected in the United States to evaluate the effect of shipping and storage.
2. Comparison of different types of plastic bags used for collection, transportation and storage of whole blood.
3. Comparison of whole blood collected and shipped in plastic bags and blood which was similarly processed in standard blood bank bottles.

Studies of Blood from the United States. This group consists of blood collected in the United States in standard bottles using ACD solutions. Samples were obtained from regular shipments to the Far East Command.

Plasma potassium and hemoglobin values are presented in Table 1. There is a regular, almost linear, rise of plasma potassium with time which may be extrapolated to 4.0 mEq./liter at time of drawing. The rise continues to approximately 20.0 mEq./liter on the twentieth day and thereafter rises more slowly to reach 24.0 mEq./liter on the thirtieth day. Individual specimens showed a relatively small scatter about the mean and the standard deviation appeared independent of the age of the blood.

Plasma hemoglobin levels showed a much wider scatter between individual observations; there was an average rise from 10 to 15 mg. per 100 ml. on the fifth day to 100 mg. on the twentieth day. When an attempt was made to compare plasma hemoglobin and potassium values, only an approximate correlation with occasional marked difference was noted on individual specimens. The two often appeared to vary independently.

Osmotic fragility of red cells showed a considerable variation between samples and could not be accurately correlated with the age of the blood. The mean of the examination of 10 units of blood in each sampling at the saline concentration of 0.6 per cent as suggested by Sack *et al.*[2] indicates increased fragility of red cells with time in the Tokyo-examined blood and also in that blood examined in Korea (Table 1).

Comparison of Different Types of Plastic Bags. Three separate shipments of plastic bags were received and examined. These included two types of plastic bags and different ACD concentrations as follows:

Identification	*Description*	*Anticoagulant Solution*
Group 1	Cutter Bag	120 ml. ACD, NIH Formula "B"
Group 2	Fenwal Bag	75 ml. ACD, NIH Formula "A"
Group 3	Fenwal Bag	120 ml. ACD, NIH Formula "B"

Table 1. Plasma Potassium and Hemoglobin and Osmotic Fragility of Whole Blood Shipped From the United States in Bottles

		Plasma K (mEq./1.)		Plasma Hb. (mg. per 100 ml.)		Osmotic Fragility % Hemolysis in 0.6% Saline
Age (Days)	No. of Samples	Mean	Std. Deviation	Mean	Std. Deviation	
Studied in Tokyo						
5	10	9. 1	1. 5	16	7	8
6	10	10. 9	2. 5	17	6	3
8	10	9. 5	1. 8	38		4
10	10	11. 9	3. 5	30	20	10
12	10	13. 0	1. 3	23	13	11
14	10	15. 5	3. 0	62	39	11
16	10	19. 4	6. 6	134	104	10
18	10	18. 3	2. 7	83	58	17
20	10	19. 4	4. 0	143	67	23
22	10	18. 3	3. 5	79	74	28
24	10	20. 6		79		26
26	8	19. 2	2. 3	79	69	40
28	8	19. 7		108		23
30	10	23. 4	3. 4	194	70	38
Studied in Korea						
*7 5	9. 9		5	52		3
9 2	11. 2		2	76		
11 9	14. 0	2. 0	13	61	60	7
13 10	14. 5	2. 3	13	68	21	8
15 10	16. 5	1. 4	10	66	50	6
17 11	16. 6	2. 9	13	43		8
19 9	18. 2	1. 6	15	87		17
21 9	19. 0	2. 3	11	113		7
25 3	20. 3		11	142		12
30			10	209		

*Blood collected in Japan.

Results of these examinations are reported in Table 2. On gross examination small clots were noted in three specimens of Group 3 (two of them 6 days old and one 10 days old) and small coagulated masses, thought to be fibrin, which disappeared on mixing were seen in most specimens of Group 3 examined in Japan. Examinations in Korea did not note any such phenomena.

Table 2. Blood Stored in Plastic Bags

			Plasma K	Plasma Hb.	Blood Glucose	Osmotic Fragility % Hemolysis in 0.6% NaCl
Group	Age (Days)	No. Samples	(mEq./1.)	mg./100 ml.	mg./100 ml.	
A. Studied in Tokyo						
1	6	2	9.4	10	316	8
1	8	2	11.2	22	321	6
1	10	2	12.2	22	287	2
1	12	2	14.0	20	333	2
1	14	2	14.4	32	260	4
1	16	2	18.4	94	285	2
2	6	2	14.4	96	390	17
2	8	2	14.5	46	372	7
2	10	2	23.5	64	380	8
2	12	2	17.3	57	332	17
2	14	2	18.7	86	327	9
2	16	2	24.5	97	313	18
3	6	2	14.4	5	605	
3	8	2	19.2	16	558	
3	10	2	23.4	40	543	
3	12	2	23.4	39	572	
3	14	2	27.0	43	553	
3	16	2	29.3	56	456	
B. Studied in Korea						
1	4	4	8.8	15	346	2
1	11	4	15.2	15	358	4
1	20	4	21.6	35	310	4
2	5	4	15.0	18	332	8
2	11	4	20.9	52	248	
2	21	4	31.5	145	309	17
3	10	12	21.9	12	615	
Estimated Standard Deviation			10%	50%		

In Group 1 the plasma hemoglobin rose from approximately 9.0 mEq./1. on the fifth day to 21.5 mEq./1. on the twentieth day, which is similar to the rise noted in bottled blood. Groups 2 and 3 show a more rapid rise in plasma potassium. Group 2 rose from 12.0 mEq./1. on the fifth day to 24.0 mEq./1. on the sixteenth day and Group 3 rose from 15.0 mEq./1. on the sixth day to 30.0 mEq./1. on the sixteenth day. The control bottled blood rose from 9.5 mEq./1. on the sixth day to 16.5 mEq./1. on the sixteenth day.

The relationship of plasma hemoglobin to time was not as sharply defined as plasma potassium. The increase in plasma hemoglobin was generally slower in the plastic bags than in the bottled blood.

Red cell osmotic fragility examinations are probably not adequately sampled to demonstrate a mean difference. Before the fifteenth day all groups are similar to bottled blood and after this time Group 1 appears lower. Group 2 and Group 3 were not examined after 16 days.

Comparison of Whole Blood Collected and Shipped in Plastic Bags and Blood Similarly Processed in Standard Blood Bank Bottles. A shipment of 24 Fenwal plastic bags and 24 Baxter bottles of group O whole blood, preserved with 120 ml. NIH formula 1 ACD solution, was received for examination. Each of these units of blood was stored at normal blood-bank temperatures and sampled on alternate days. The bloods were collected in the Zone of Interior and handled by the normal channels for blood shipment. The plastic bags were 5 days old when received and the bottles 6 days.

Plasma potassium (Fig. 1) was higher in the bags on initial examination and increased more rapidly for the entire period of examination when compared to the bottled whole blood. The rate of change in both bags and bottles was a steady one with the bags showing 13.4 mEq./1. plasma potassium on the fifth day and 36.9 mEq./1. on the thirtieth day. The bottled whole blood showed 11.2 mEq./1. on the sixth day and 24.4 mEq./1. on the thirty-first day of examination. Standard deviation of each lot was relatively constant for the entire period of examination, with more than 90 per cent of each sampling falling within one standard deviation from the mean.

Plasma hemoglobin values (Fig. 2) were slightly higher in the bottled blood until 16 days, after which time the blood in the plastic bags showed accelerated hemolysis. The blood in plastic bags showed a gradual increase from 5.3 to 29.2 mg. per 100 ml. hemoglobin between the fifth and fifteenth day and then climbed rapidly to 231 mg. on the thirtieth day. The bottled blood showed 10.7 mg. per 100 ml. hemoglobin on the sixth day and 32.6 mg. on the sixteenth day. Rate of increase was not as rapid in the bottles as in the bags after 16 days and at 31 days the plasma hemoglobin of the bottled blood was 112 mg. per 100 ml. Standard deviation in both samplings increased with age of blood. Most of the values fell within one standard deviation from the mean.

Osmotic fragility (Fig. 1) of the red cells in the plastic bags was, as a rule, lower than that of the bottled blood. After 15 days the blood in the bags showed decidedly less hemolysis in 0.6 per cent saline than that preserved in the bottles.

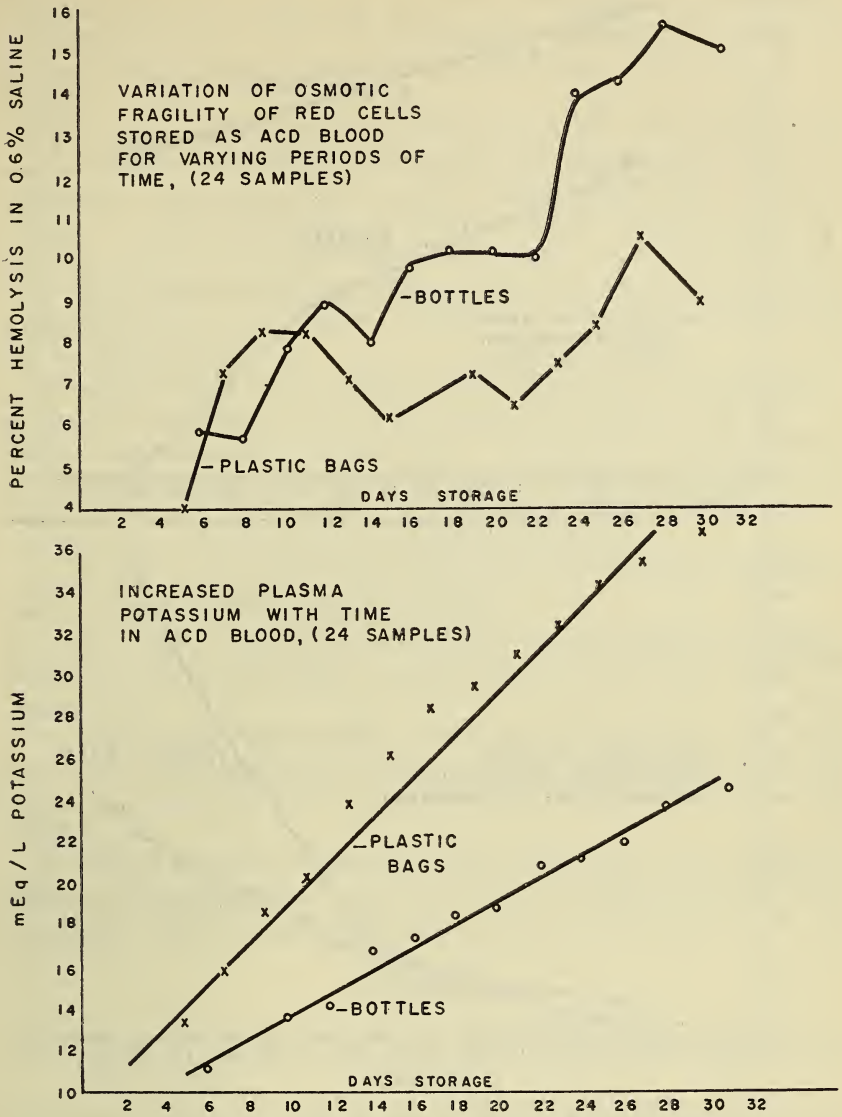

FIGURE 1.

Whole blood glucose (Fig. 2) in the bottles was lower at all times than in the bags. Apparently, a different lot of ACD solution had been used in the two types of containers. The glucose in the bottled blood decreased at a steady rate through 22 days and then its consumption was apparently accelerated for some reason. This did not

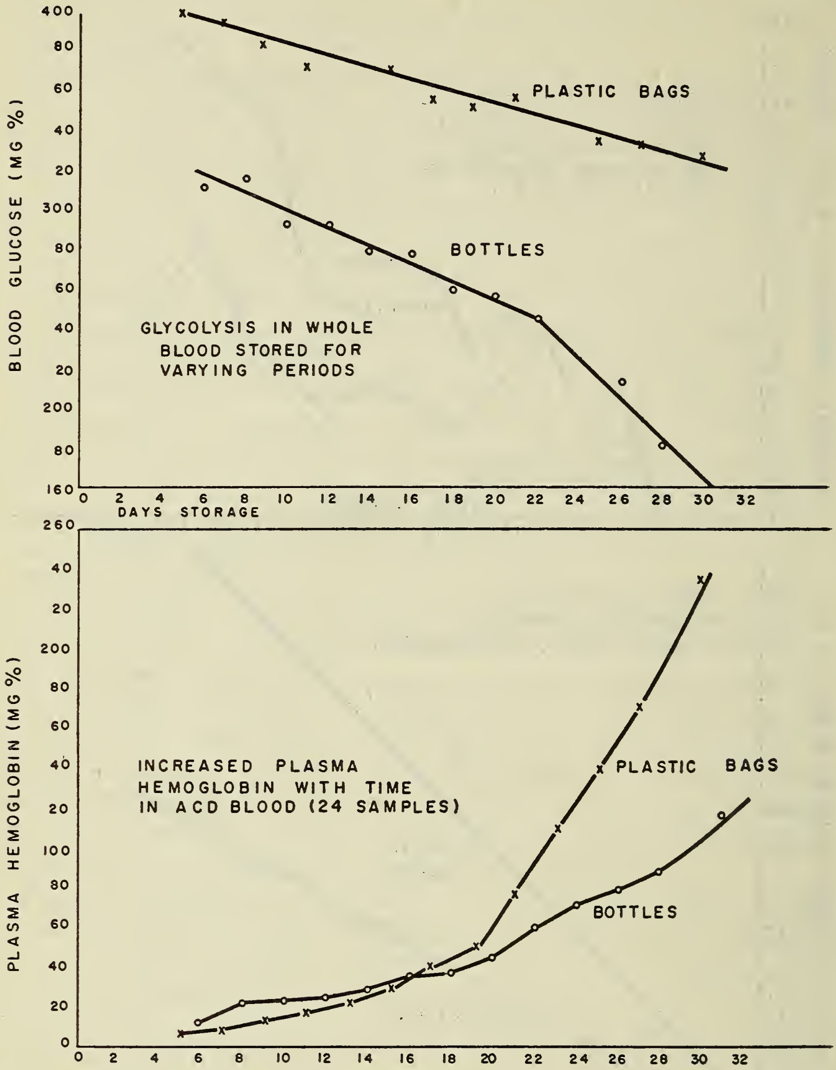

FIGURE 2.

occur in the bag blood, which continued glycolysis at approximately the same rate for the entire period of testing.

Summary and Conclusions

A regular, almost linear rise in mean plasma potassium was noted with time. The rise continued to approximately 20.0 mEq./1. on the twentieth day and thereafter rose more gradually to reach 24.0 mEq./1. on the thirtieth day. The plasma potassium could be extrapolated to 4.0 mEq./1. at the time of bleeding. The individual specimens showed a relatively small scatter around the mean with the standard deviation apparently independent of the age of the blood.

Plasma hemoglobin levels in bottled blood showed a much wider scatter between individual observations with the standard deviation apparently more dependent on individual sampling than on time of storage. A rise in mean plasma hemoglobin was noted from 10 to 15 mg. per 100 ml. on the fifth day to 100 mg. on the twentieth day. Only approximate correlation was noted between the rise of potassium and hemoglobin in the plasma. These two values often appeared to vary independently.

In bottled blood (ACD solution, NIH formula A) the whole blood glucose fell at a steady rate from a mean of 312 mg. per 100 ml. at 6 days to a mean of 248 mg. at 22 days. Thereafter the rate appeared to accelerate slightly until at 31 days the mean glucose level was 174 mg. per 100 ml. The blood in bags showed a similar rate of decrease, but the slope at 25 days had a tendency to level off.

Comparison of bottled whole blood and that collected in plastic bags revealed the following information:

1. The rate of diffusion of potassium was more rapid in the whole blood collected and shipped in plastic bags for the entire period of comparison.
2. The mean osmotic fragility of red cells, using 0.6 per cent saline as a point for comparison, was more stable in the whole blood contained in plastic bags after 12 days. Up to this point the results were similar.
3. Plasma hemoglobin values in bags and bottles were comparable until 18 days of storage. After this time the plasma hemoglobin in the plastic bags increased more rapidly than in the bottles.

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Chapter 11

The Blood Program in the Korean War

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Although there was no established blood bank in the Far East Command when the Korean War began, whole blood from an operating blood bank was available to the first medical field installation when it began to receive patients. Thereafter, regardless of the fortunes of war, blood was always available in adequate amounts to meet the requirements of the combat forces. This paper will describe the organization and establishment of a functioning blood bank under emergency conditions, the difficulties encountered, the policies established, the storage and distribution practices, the problem of estimating blood requirements, an analysis of the amount of blood issued, the amount actually used, and the use of group "O" blood for all patients in the field. Certain recommendations will be made based on experience during the period July 1950 to July 1953.

Organization and Mission of the Blood Bank

On 3 July 1950, responsibility for collecting and distributing blood in the Far East Command was assigned to the 406th Medical General Laboratory in Tokyo and on 7 July blood was delivered to the first hospital unit arriving in Korea. To accomplish this, personnel were diverted from other laboratory activities, available supplies and bleeding sets were obtained from depots, base and mobile bleeding sections were established, additional refrigerators were obtained, and an intensive publicity campaign to obtain donors was initiated. In August 1950, the 8090 Blood Bank Laboratory Detachment was activated and attached to the 406th Medical General Laboratory although it was long before qualified personnel were acquired. By September 1950, a more realistic appraisal of the "police action" in Korea had indicated that blood sources in Japan were not sufficient and group "O" blood was being supplied from the continental United States.

The mission of the Tokyo Blood Bank was to supplement shipments of group "O" blood from the Zone of Interior, to furnish blood of all groups and types to hospitals in Japan, to act as a blood-distributing center for the theater, to investigate blood storage, distribution and use policies and practices, and especially to furnish sufficient blood to meet emergency requirements during the time increased shipments were in transit from the United States.

Difficulties

During the early months of the war, operation of the blood bank was plagued by shortages of critical supplies. Vacuum bottles were not available in sufficient amount and it did not appear that a sufficient supply could be obtained immediately from the United States because of the high priority given to other supplies. Under close technical direction and controlled by rigid laboratory testing, selected Japanese firms produced ACD vacuum bottles, as well as disposable donor and recipient sets, which met American standards. Even pyrogen-free water became critically short, the emergency being met by continuous operation of an improvised distillation system.

Few of the staff had had prior blood bank experience but were trained as they worked. They were assisted by a group of devoted part-time volunteer workers mainly from the American Red Cross and later from the Japanese Red Cross also. These volunteers served as receptionists, nurses' aides, clerks, and in many other capacities. Certain of the volunteers conducted much of the publicity and public relations work which was so important in obtaining donors. In this activity the radio and press facilities under military and Japanese control cooperated wonderfully, as did most of the prominent visitors to Japan.

Disposal of outdated blood was a constant problem. No method was found for maintaining a reserve of a perishable agent such as blood in amounts sufficient to meet expected requirements without an appreciable portion becoming outdated. Of course this is true even in fixed civilian hospitals where the requirements for blood transfusion are much more stable than on the battlefield.[1] This was further complicated in periods of military pressure when local blood collection facilities were being strained to meet a sudden increase in blood requirements. At such times widespread appeals for group "O" donors produced many volunteers of other blood groups who could not be dissuaded from donating blood without antagonizing them and injuring the intensive drive for donors. In such periods depot stocks of groups "A" and "B" would exceed desired levels. The blood bank was directed to send the outdated group "O" blood and excess blood of other groups to Korean depots. Some of it was used apparently without harm as supportive therapy for patients with tuberculosis and prior to elective surgery in base hospitals. When Korean military hospitals were established further forward, blood approaching the outdating limit, and later fresher blood, was sent to these hospitals.

During 1952 when the combat situation was relatively stable, the usual daily shipment of blood to Korea consisted of 240 bottles of blood. During the frequent short periods of combat activity, it was not unusual to send up to 800 units of blood daily to Korea and then to send none during the lull in activity which often followed. Despite a definite informational effort to acquaint donors collectively and individually with these facts, the flow of donors could not be cut off too sharply at such times without many being offended and thus jeopardizing a favorable response to subsequent emergency appeals. Also previously increased shipments from the United States continued to arrive for a brief period after such a lull even with the earliest possible notification of reduced needs. On a few occasions persons in high authority scheduled the bleeding of large units for its publicity value to the national blood program despite the fact that there was little need for the blood at the time. With these wide fluctuations in requirements and supply, there were wild fluctuations in the amount of blood in reserve in Tokyo ranging from almost none to over 2,000 units.

The Japanese medical profession seldom used transfusions and there had never been a blood bank program on an appreciable scale. Nevertheless, many Japanese individuals, social groups, and labor unions volunteered as donors even before publicity was aimed at them specifically. A complication which arose was a restriction against collecting more than 200 ml. of blood from any of these donors. With the support of the Japanese Medical Association, the 200 ml. limit was replaced by a table of comparative values which established the volume of blood to be collected from persons of small stature. The relatively lower incidence of group "O" and the invariable presence of the Rh factor limited somewhat the full applicability of this large donor group to recipients whose distribution of blood group and Rh type was somewhat different.

Policies

The general policy was established that only group "O" blood would be sent to Korea. The antibody titer was indicated on the label in order that high-titer blood would be used on "O" recipients only, while that of low titer could be used for all patients. Although all blood was labeled as to Rh type, no attempt was made in Korea to determine the recipient's Rh factor, it being felt that serious reactions on the basis of Rh incompatibility were unlikely in battle casualties. The calculated risk obviated the need for maintaining separate supply levels and recognized the emergency nature of the use of blood in combat surgery. The hospitals in Japan determined the group and type of all patients prior to transfusion and used compatible blood which was further checked by crossmatch.

Storage

Blood was considered to be outdated 21 days after collection, and this expiration date was printed on the label. Investigation late in 1952 indicated that blood deteriorated fairly slowly during the first 10 to 14 days of storage and thereafter more rapidly. Even before this, measures had been instituted to get fresher blood to the patient. When it was pointed out to them, medical supply officers at the depots quickly recognized that the usual supply practice of "first in, first out" did not apply to blood because that practice resulted in putting fresh blood on the shelves while old blood was sent to the hospitals. However, the attempt to give fresher blood aggravated the problem of trying to reduce the amount of blood becoming outdated and at the same time maintaining reserves for emergencies. This problem was further complicated by the establishment of multiple reserve depots (see below). Early in 1952, the blood on the average was 18 or more days old when it was given to the patient, but by the end of the year, this had dropped to about 14 days.

The necessity for maintaining blood at a constant low temperature was recognized at all installations. At first, batteries of miscellaneous small refrigerators had to be used. Later, large walk-in refrigerators became available at major depots. All installations maintained a close watch for fluctuation of temperatures in the refrigerators by frequent periodic inspections of thermometers in the refrigerators or the use of constant recording thermometers. Despite this, there were two or three instances when the entire reserve at an installation was destroyed because thermostat failure resulted in freezing overnight.

Refrigeration During Shipment

Various expedients were used to maintain refrigeration during shipment of blood. In all methods, wet ice was placed in a separate metal container in close proximity to the bottles of blood. At first, standard "marmite" food containers were used. These were bulky, heavy, could hold only a few bottles of blood and were seldom recovered from the receiving unit in the field. Later, insulated plywood boxes with hinged tops, metal racks for 16 bottles of blood, and a central metal container for ice were used. These withstood moderately well the rigors of exposure to weather and rough handling, and were not well suited for other purposes so that almost all were returned. Temperature below 10° C. was maintained in these boxes for at least 24 hours with one filling of the ice container, which was easy to reach if re-icing was necessary. These containers were used for the shipment of blood to all depots and medical using agencies within the theater. More elaborate but similar trunklike containers were developed in the United States for the shipment of blood to the Far East Command.

Distribution

The blood bank in Tokyo was responsible for the distribution of all blood in the theater. It, therefore, maintained a large reserve to meet any contingency. Routine shipments of blood were received six times a week from the United States, one of the shipments being twice as large as any of the others. Although, in emergency, additional blood could be obtained from the Zone of Interior within 48 hours, it was assumed for planning purposes that 4 days would elapse between the time a cable was sent to the Armed Services Blood and Blood Derivatives Group for additional blood and the arrival of the blood in Tokyo. During this time, the blood bank, by using its reserves in Tokyo and by increasing activity of the bleeding teams, was responsible for providing the required blood. It was estimated that the Tokyo depot could send to Korea 3,500 units of blood during the 4-day maximum waiting period for increased shipments to arrive from the United States.

Until the early months of 1951, the hospitals in Japan received patients who had been wounded only a few hours or days before. During this time, these hospitals required large amounts of blood. Two sub-depots were established to meet these needs. One supplied the hospitals in Southern Japan and served as an emergency depot for the Pusan area while the other served the hospitals in the Osaka area. These sub-depots received their blood from Tokyo by rail, a baggage car having been equipped with refrigerators for this purpose.

The blood sent daily by air to Korea was accompanied by a courier who, at first, made delivery direct to hospitals. Later, the shipments were taken to the medical supply depot which then assumed responsibility for proper storage and distribution in the combat zone. This in turn made the depot commander responsible for the availability of an adequate supply of blood, forcing him to maintain reserves of blood to meet emergency situations. After the landing at Inchon and the break-through from the Pusan area, independent depots were maintained in Pusan and Seoul. The Seoul depot subsequently established two sub-depots which in turn maintained reserve supplies.

Blood from Tokyo reached Seoul 8 to 12 hours after being requested. The sub-depots in the Eighth Army area could receive blood from Seoul in 2 hours if weather permitted air transport, with a maximum of 8 hours under adverse weather conditions. The hospitals could obtain blood from the sub-depots in an hour or less. As the time required for receiving blood decreased, smaller reserve stocks were maintained. However, there was a limiting factor which was related to the psychology of preparedness. There was always the realization that although excess amounts of blood were undesirable, inadequate amounts were disastrous. Just as the soldier who has used his tenth grenade on a combat patrol will not willingly carry less on his next foray, so the commander who has seen 100 units of blood administered in a single influx of casualties will not decrease a high blood reserve until assured that active combat has definitely subsided and will not suddenly re-appear.

Estimating Blood Requirements

When the blood bank was first established, a search was made for a method of estimating blood requirements. The single reference available[2] reported that the British, based on experience in the Middle East, recommended using 0.1 unit per soldier wounded in action (WIA); that the data from U. S. Forces in the Mediterranean Theater indicated that 0.45 unit was used per WIA; that the whole Blood Committee of the European Theater of Operations utilized for planning purposes 0.2 unit of blood per casualty (type not stated). Experience during the first 5 weeks of the war in Korea indicated that 0.8 unit of blood per WIA was required, a much higher figure than any previous estimate but due to rise even higher.

In view of the build-up in troop strength in Korea projected for the period August 1950–February 1951, a long-term estimate of casualties was attempted. It was assumed that heavy combat losses would continue until UN Forces gained tactical superiority; losses would then be at a moderate rate but still increasing for an additional period as the size of our forces continued to grow. Finally, enemy resistance would be overcome, guerilla and police action might continue, and noncombat injury would become of relatively greater importance. Applying the factor 0.8 pint/WIA, blood requirements for the 6-month period could be expected to increase gradually with a maximum to be reached in October 1950. These estimated requirements far exceeded the estimated 100 units per day which could be collected over a prolonged period by repeated donations from the 20,000 potential donors in the Tokyo-Yokohama area. A request was therefore made that group "O" blood be sent from the United States and this request was promptly honored.

As the war progressed, it became increasingly difficult to plan blood bank activities on the basis of daily intelligence reports. The changing tactical situation was accompanied by changes in the medical support program. Hospitals in Japan lengthened their evacuation policy and more frequently used blood for treatment of nonbattle casualties and disease. Medical organizations in Korea insisted on maintaining high stock levels of blood. Since these could be depleted as readily by outdating as by use, requests for additional blood did not always reflect battle activity. Throughout the war, there was a constant and progressive increase in the percentage of battle casualties transfused and in the amount of blood used in the treatment of war wounds.

In 1952 and 1953 local actions, probing attacks, and defense of strong points characterized the fighting. There were few offensives and these were limited and of short duration. Often it was the enemy who determined the combat area and severity of the fighting. Consequently, short-term prognostications of the number of combat casualties to be expected became less reliable.

As a result of the interplay of these various factors, attempts to prognosticate needs for blood on the basis of expected combat activity were largely abandoned. They were replaced by a policy of obtaining sufficient blood to meet requests and maintaining a reserve in Tokyo of 800 to 1,200 units of blood. On the few subsequent occasions when blood was obtained in anticipation of requirements, results were quite poor. However, it is still believed that planning for blood requirements is a logical method of blood bank operation and that, under a different situation and with due allowance for the modern more liberal use of blood in treating battle casualties, this method would be successful.

The desirability of giving patients blood as fresh as possible complicated the attempts at estimating blood requirements and maintaining a blood reserve. In theory, the Tokyo Blood Bank would extract about 50 units of blood from the amount received each day, putting these units in the reserve and replacing them with blood 15 or 16 days old. This group of fresh and old blood would be sent to the depots in Korea where the old blood would be used to replace reserve blood which had become outdated, while the fresh blood would be given to patients. In practice, the need for blood was rarely constant, but rose and fell like great and unpredictable tidal waves. It was necessary not only to record the amount of blood on hand but also the expiration date of every unit to guard against the possibility that the entire reserve would become outdated at one time if it had accumulated during a quiet period.

Issue of Blood

In 1950 and the first half of 1951 recently wounded patients often received first definitive care in hospitals in Japan. During a 3-month period in 1950, 77 per cent of battle wounded were evacuated to

Japan while during a similar period at the end of 1951, 48 per cent were evacuated to Japan. It is not known what percentage of the blood sent to hospitals in Japan was used for the treatment of battle casualties but an indication that much of it was not used for the immediate treatment of the battle wounded is seen in the fact that these hospitals requested almost as much blood in the first half of 1952 when casualties were lowest as in the second half when twice as many casualties occurred (Fig. 1). In the 3 years covered by this report, approximately 18 per cent of the blood distributed by the Tokyo Blood Bank went to hospitals in Japan.

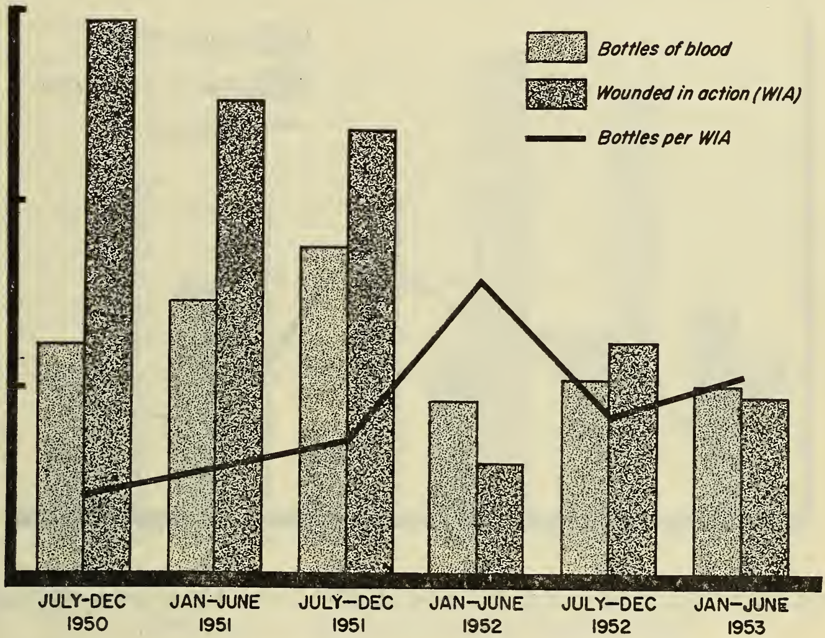

FIGURE 1. Blood supplied to hospitals in Japan in relation to wounded in action—United Nations Forces less those of Republic of Korea (UN less ROK).

In Korea, during 1950, most of the field hospitals were in the Pusan area, and of necessity primarily served to render casualties transportable as soon as possible to Japan. Throughout most of 1951 the hospitals of Eighth Army were more numerous, widely dispersed, and played a larger role in the care of wounded. By 1952 the hospitals in the southern part of Korea played a less prominent role in the care of battle casualties. In August 1952, the southern three-fourths of the Republic of Korea (ROK) was designated a communications zone and the northern portion was assigned to Eighth Army as a combat zone.

In Figure 2, the blood sent to all of Korea in 1950 and 1951 was considered as sent for the treatment of battle casualties while thereafter only the blood sent to Eighth Army was so considered.

It was not possible to determine from the available information what portion of the blood issued was actually used for the treatment of battle casualties. However, it is of greater importance for blood bank operations to determine how much blood must be supplied per battle casualty. Unfortunately even this simple calculation could not be made accurately, because, after 1951, increasing numbers of Korean troops were assigned to U. S. forces and received treatment in U. S. hospitals and at the same time blood was sent to some but not all of the ROK field hospitals. Korean doctors did not use blood as liberally as American doctors, and they did not make direct requests for blood but received available blood which was in excess of the requirements of U. S. hospitals. Consequently, inclusion of all ROK casualties to whom blood was not always available decreased the ratio of blood supplied per casualty while omission of ROK casualties removed a significant number who received such treatment. During a 2-week survey in 1952, 29 per cent of blood transfusions in American hospitals in Korea were given to Korean troops most of whom were attached to American units; during this time 70 per cent of all casualties were Koreans. It has been estimated that from 20 to 30 per cent of the blood received by Eighth Army depots in 1952 and 1953 was sent to

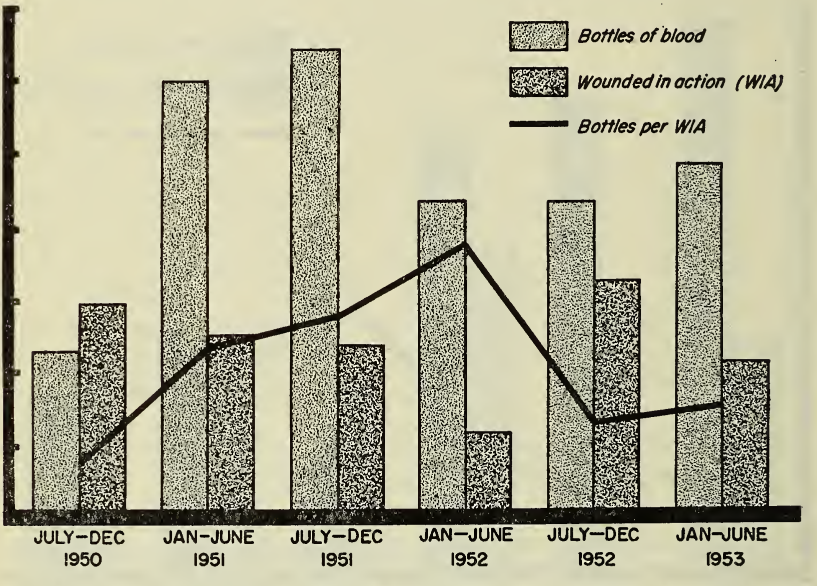

FIGURE 2. Blood supplied to Korea in relation to wounded in action (UN less ROK through December 1951; total UN thereafter).

ROK hospitals and approximately 50 per cent of the blood sent to Eighth Army was used for the treatment of ROK casualties. However, a firm policy for supply of blood for Korean casualties was never established. Some blood was requested with the intent of sending it to ROK hospitals but much of the blood sent to Eighth Army was originally requested for U. S. Army hospitals and would have been destroyed because of outdating if not sent to the ROK hospitals.

Omitting the build-up phase of 1950 as not representative, between 2.10 and 3.39 units of blood were supplied to the combat zone for each casualty incurred (January 1951 to July 1953). Even the lower of these two figures is greatly in excess of rates of actual use of blood to be discussed later.

One of the reasons for the apparent issue of blood to Korea in excess of the amount used is the need for maintaining reserves. Without changing the reserve level, there are many more units of blood per casualty in reserve when the casualties are few than when the number of WIA is large. Further, when there are many casualties there is a much more rapid turnover of blood in stock, the reserves are used more efficiently, and there is little outdating of blood. At such times, consequently, a greater proportion of the blood is actually used for the treatment of casualties.

When the combat zone data are charted monthly (Fig. 3), an inverse proportion is evident between the number of casualties and the issue

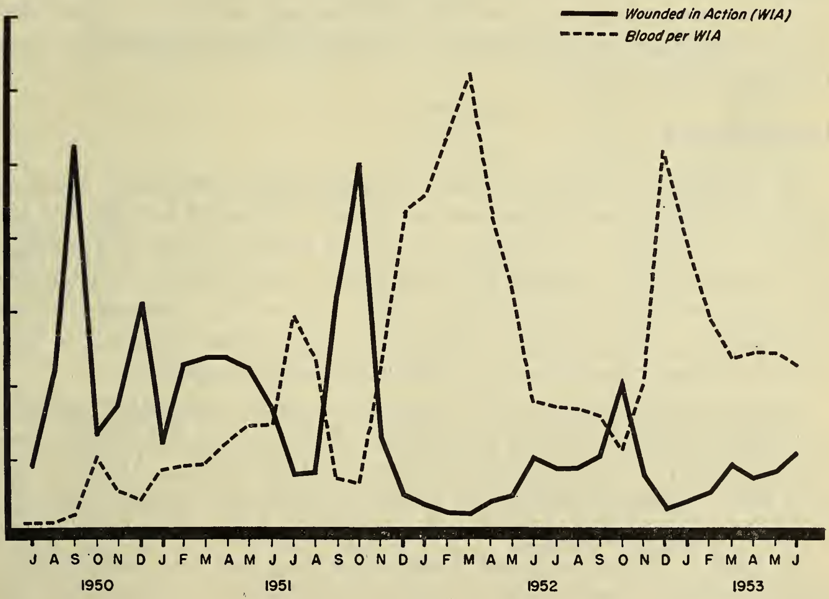

Figure 3. Blood issue factor in relation to wounded in action by month (UN less ROK).

factor of bottles of blood per casualty (B/WIA). This emphasizes that it was the maintenance of reserves at a high level which determined the amount of blood issued to Korea and that during periods of activity only a relatively small additional amount was needed.

Three factors determined the reserve level. One, already mentioned, is the psychological attitude that the maximum amount of blood required at any time must always be available. The second factor is the time required for replenishing the blood reserve. The possibility that bad weather will increase the time required for transportation of blood is an important consideration in determining how much blood must be available. The third factor is the number of organizations maintaining reserves of blood. There were as many as five stores of blood between the donor in the U. S. and the wounded soldier in Korea: the processing center in California, the blood bank in Tokyo, the depot in Seoul, the sub-depot in the corps area, and the surgical hospital blood bank. Each of these maintained reserves for emergencies. The amount of blood which would have been destroyed because of outdating would have been great were it not for the fact that the California depot could divert unneeded blood to fractionation centers and the depots in the Far East Command could give it to the ROK hospitals that needed it. The magnitude of this problem is indicated by the fact that during a period of intense combat activity there was available in the theater more than 12 times the average daily amount given to casualties other than ROK and more than 5 times the maximum amount given these casualties on any one day. Under other circumstances, the multiplicity of stores of blood would have been inefficient and wasteful.

Use of Blood

It is difficult, during combat, to determine how much blood is actually being given to the war wounded. Detailed records are not maintained and are often inaccurate when large numbers of casualties are received. The amount of blood given a wounded soldier depends not only on the severity of his injury but on the type of medical installation. The surgical hospitals give more blood per patient than do the division medical units or the evacuation hospitals.

During 1950 and part of 1951 recently wounded soldiers were treated in hospitals both in Korea and Japan. No estimate is available concerning blood use during the early part of this period. Applying the best data available during the period 1 April—31 August 1951, 0.6 unit was used in Korea per battle casualty admitted to hospitals.

In 1952 a survey of blood distribution and use was conducted in Korea during a 2-week period when our forces were experiencing the largest number of casualties received during the year. Information was obtained in two ways. The medical units listed the number of casualties received and the number of units of blood given to patients who were identified by name, rank and serial number. At the same time machine records casualty reports were studied which listed by name, rank, serial number and organization, all U. S. Army casualties during this period. Two months later the status of each of these patients was reviewed. With this information, it was possible to determine (1) how blood was used in medical installations at different levels in Korea, (2) the amount of blood given to Korean troops treated in U. S. Army hospitals, (3) the amount of blood given to casualties in relation to the duration of disability as a measure of the severity of injury, (4) the average amount of blood actually used in the treatment of battle casualties, (5) the tendency to use low-titer blood in preference to high-titer blood, and (6) incidence of transfusion reactions.

For the purpose of this survey, the Mobile Army Surgical Hospital (MASH) was considered as a Corps unit and the evacuation hospital as an Army unit. One of the evacuation hospitals was also the Renal Failure Center, and used a proportionally larger amount of blood because of this function.

The survey indicated that approximately 20 per cent of all wounded in action received blood transfusions at an average rate of 4.3 bottles per transfused patient or 0.9 bottle per total U. S. wounded. In Table 1 this information is given for the medical installations at different levels and for Eighth Army as a whole, based on casualty reports of U. S. Army war wounded only.

Table 1. Blood Use Factors by Echelon of Medical Care

	Per Cent of WIA Transfused	No. of Bottles Per WIA	No. of Bottles Per Patient Transfused
Division level	2. 0	0. 09	4. 4
Corps level	29. 3	0. 99	3. 4
Army level	5. 4	0. 15	2. 7
Total 8th Army*	20. 2	0. 9	4. 3

*Corrected for admission to and transfusion in more than one unit.

At the time of the survey, divisional medical units used little blood proportionately, possibly because the large influx of casualties did not permit extended care of severely wounded at that level. An exception, not included above, was the Medical Battalion of the Marine Division whose medical companies function in a manner comparable to a MASH. It was understandable, therefore, why 29 per cent of casualties admitted to such USMC installations were transfused. Most of the blood in the combat zone was used by MASH's in keeping with the primary mission of these hospitals to provide resuscitation and initial surgery to nontransportable, severely wounded. In fact, the more severely wounded frequently were flown directly by helicopter from the battalion aid station to the MASH, by-passing other division medical units. Although all of the severely wounded patients were sent ultimately to the evacuation hospitals, this generally was not effected until resuscitation and immediate surgery had been accomplished. For this reason and because of the number of transportable, less severely wounded moved directly from clearing station to evacuation hospital, a much lower percentage of those admitted to the latter installations required transfusion.

During the period of this survey, more than 1,500 U. S. Army troops were wounded in battle. Analysis revealed that 21 per cent were seriously wounded and 79 per cent lightly wounded. When records on these patients were analyzed 2 months later (Table 2), 3 per cent of the wounded had died, another 3 per cent originally considered seriously wounded had been returned to duty, and 15 per cent also seriously wounded were still hospitalized. At the same time 34 per cent of the wounded were still hospitalized despite an original categorization as lightly wounded. The amount of blood given with relation to severity of injury is given in Table 2.

Table 2. Blood Use by Severity of Wound

Category	Per Cent of Total WIA	Per Cent of Category Transfused*	Units of Blood Per WIA	Units of Blood Per Patient Transfused
Died of wounds (DOW)	2. 8	**55. 1	7. 0	12. 7
Seriously wounded	15. 1	69. 0	3. 1	4. 4
Seriously wounded returned to duty	3. 4	13. 6	0. 4	3. 0
Lightly wounded	34. 1	17. 8	0. 5	2. 6
Lightly wounded returned to duty	44. 5	3. 8	0. 08	2. 2
All cases		20. 2	0. 9	4. 3

*Corrected for admission to more than one medical unit.

**20% DOW known not to have received blood and 25% DOW may have received blood but not identified by name on any transfusion records.

The large amount of blood given to 69 per cent of the seriously wounded is not surprising but that almost 4 per cent of the lightly wounded returned to duty should get an average of 2.2 units of blood indicates how freely transfusions of whole blood were given.

During the period of survey, there was a definite tendency to use low-titer blood for all patients although this in part was regulated by the amount of low-titer blood locally available. Thus 72 per cent to 82 per cent of Koreans whose blood type was unknown were given low-titer blood while 60 per cent to 80 per cent of U. S. troops whose blood type was recorded on blood tags were given low-titer blood. If there was excess blood at an installation, it was the high-titer blood which was retained in the reserve.

The survey also showed that under combat conditions, very little attention was paid to the possibility of transfusion reaction. Only 2.5 per cent of the patients transfused were reported to have had reactions and these were all of the minor urticarial or febrile type. One hospital which treated only 7.5 per cent of the patients transfused reported 58 per cent of these reactions. Although serious transfusion reactions often cannot be detected in patients in severe shock or under anesthesia, the general evidence based on autopsy studies, postoperative hospital course, reactions in lightly wounded casualties and the investigations at the Renal Failure Center all indicate that little hazard was attendant on the use of group "O" blood for all casualties.[3] The advantage of having blood immediately available for resuscitation without the necessity for waiting for a laboratory procedure more than outweighed the potential hazard.

Discussion

Adequate prior plans had not been prepared for the unexpectedly sudden attack on South Korea and our precipitate involvement under United Nations urging. Such a situation may recur and with the possibility of atomic attack, our medical concern may well be with our homeland. Since it is not feasible to maintain on a stand-by basis military units such as blood bank laboratory detachments or blood bank bleeding detachments, the alternative would be to assign the responsibility for the emergency establishment and operation of a regional blood program to a suitable medical unit in each overseas command and at strategic locations within the continental United States. Each responsible medical unit should be required to formulate appropriate plans, and to ascertain that sufficient supplies and equipment are available at a known depot. Such an emergency function cannot be continued indefinitely, however, and plans should extend to the rapid mobilization of the proper units capable of assuming blood program responsibilities.

The Korean War was not one of the major military operations from the standpoint of size in this century of world wars. Accordingly, it is not surprising that adequate amounts of blood were always available. In World War II rationing of blood was necessary on occasion,[2,4] and in future catastrophes it may again be necessary. In such an event it is essential that one individual be responsible to the area surgeon for the adjustment of supply of blood to demand by control of collection, requisition, storage and distribution.

Experience in the Korean War suggests that a blood program of greater efficiency would have resulted had responsibility for the entire area been assigned to one organization under the command of a medical officer qualified to supervise blood collection, storage, distribution and use. It is furthermore felt that then any limitation on availability of blood would have been charged properly to that individual rather than to the medical depot commander, whose responsibility would appear to be limited more reasonably to providing refrigerated holding facilities for the blood.

The centralization of all blood collection within the theater was dictated initially by supply problems and limited donor sources. Later, large hospitals in the rear areas should have been encouraged to organize their own blood program with locally available donors and facilities. Assistance and some continuing supervision would doubtless have insured satisfactory operation. Further exploitation of local resources by use of multiple collecting centers or by means of a railway collecting unit was considered, and could have been used to meet total requirements. This would have greatly increased the role of the supervising and coordinating agency, however. Such plans were not put into use because of the lack of a suitable means of plasma salvage within the theater, and because of the desirability of continued integration with the national blood program.

In many hospitals in Korea surgeons held that fresh blood that was type specific was greatly to be desired over stored blood from universal donors. Under combat conditions in the field, however, this is not only hazardous but impractical, the feasibility of satisfying such a desire disappearing rapidly within an army zone. In addition, it was conclusively demonstrated that type-specific blood, such as group "A", should not be given to a patient of that type if he had recently received multiple transfusions of group "O" blood in forward hospitals.[5]

It is evident that the trend is towards more liberal use of blood. When indicated, blood transfusions are of great value in the treatment of the wounded. However, indiscriminate and excessive use of blood as a sort of harmless medical insurance is not without danger because, despite all efforts, there is the possibility of human error in typing and labeling blood and because of the possibility of immunizing the recipient unnecessarily through Rh or other factors in the blood.

Consideration of future situations entailing a shortage of blood emphasizes the need for improved methods of preservation of blood, for improved plasma expanders, and for a re-evaluation of the minimum amount of whole blood required for resuscitation. Plastic blood containers, given preliminary evaluation in Korea, appear highly promising and are being constantly improved. They could materially alleviate part of the logistic problem described.

Conclusions

1. In each overseas major command plans must exist for immediate implementation of a blood program. This should include designation of a specific unit as responsible for the planning and emergency operation of this activity including estimation of requirements, and methods of collection, storage and distribution.
2. For planning purposes, 0.9 unit of blood per WIA per day times the number of days required to replenish stocks appears to be a reasonable supply level for an overseas theater. Whether this amount can be met will depend on the size of the military operation, education in the use of blood substitutes, and over-all national requirements.
3. With a perishable commodity such as blood plus the suddenness with which daily requirements may vary, local resources should be developed to a maximum degree.
4. The distribution system for blood should be based on the most direct system of supply feasible with a minimum number of storage centers.
5. A continuing program in professional education and supervision of the use of blood and plasma expanders should exist within the theater.

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Chapter 12

Plasma Retention and Urinary Excretion of Dextran and Modified Fluid Gelatin in Combat Casualties*

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Limitations in the availability of whole blood forward of the surgical hospital as well as the subsequent occurrence of homologous serum hepatitis following the administration of dried human plasma have repeatedly complicated the clinical management of the combat casualty. Following the successful use of dextran and modified fluid gelatin in experimental animals and in surgical patients,[8] these materials were made available to forward medical units during the Korean conflict for evaluation of their effectiveness as resuscitative and supportive agents. Further evaluation was necessary since the fate and the limitations of use of these compounds in severely injured patients had not been sufficiently investigated. In addition, the potential usefulness of such information in managing casualties of future disasters was obvious.

Purpose

To substantiate the clinical observations on the effectiveness of dextran and gelatin in combat casualties,[1, 2] certain metabolic studies were necessary. It was believed that measurement of the circulatory retention of the plasma expander would be the best index of the degree and longevity of circulatory support. Measurement of urinary excretion rates would offer an index of the method of elimination as might be affected by marked circulatory, renal [10] and metabolic disturbances

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*Previously published in Surgery *37*:384, 1955.

accompanying massive trauma and hypotension. Of basic importance for the management of combat casualties was the relationship of effective circulatory support to evacuation time. During the period of this study (January–August 1953) the average evacuation time was approximately 3.5 hours, and these experiments were designed to evaluate the potential use of dextran and gelatin as the sole supportive agents during evacuation.

Materials and Methods

Of the several hundred patients who received dextran or gelatin, 16 of the seriously wounded dextran patients and 10 of the seriously wounded gelatin patients were selected for this study. The dextran used was a product of the Commercial Solvents Corp., Lot 250 R2, having an average molecular weight of 42,000,* the modified fluid gelatin was a product of the Knox Gelatine Company, Lot MFG #9, having an average molecular weight of 34,000.**

All patients studied were young, male, United Nations combat casualties with injuries from artillery, mortar, grenade, land mine, or small arms fire. Some appeared *in extremis* upon admission—with imperceptible pulse and blood pressure. In general, they represent the type of casualty that required immediate blood replacement and extensive surgical treatment. Table 1 demonstrates the wound distribution in the patients studied.

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*Molecular weight determination by Research Unit, Fort Totten, N. J.

**Molecular weight determination by University of Wisconsin.

Table 1. Distribution of Wounds in 26 Combat Casualties Used for Metabolic Studies of Dextran and Gelatin

Site of Primary Injury	Sites of Additional Injuries						
	Chest	Abdomen	Amputation	Compound Fracture	Major Artery	Massive Soft Tissue	Extremity Perforation
Chest	*(1)	0	0	1	0	1	1
Abdomen	0	(15)	2	8	3	9	8
Amputation	0	2	(5)	4	2	3	5
Compound fracture	1	8	4	(14)	2	8	11
Major artery	0	3	2	2	(4)	3	4
Massive soft tissue	1	9	3	8	3	(14)	14
Extremity perforation	1	8	5	11	4	14	(20)

*Figures in parenthesis indicate total sustaining specific wound.

An attempt was made to follow a strict protocol, but in the majority of instances deviation from the protocol was necessitated by the patient's condition. Nevertheless, the unanticipated complications, although destroying certain uniformity, were invaluable in determining the effectiveness and role of these expanders in the treatment of severely wounded.

In general, the procedure employed was as follows: Upon admission, all patients received immediate resuscitation and operation was initiated only after blood volume replacement. Support of the circulation with whole blood continued during the operative procedure. Immediately after operation a plasma volume determination was performed (T–1824), and the infusion of the plasma expander started. The time of the infusion varied, in accordance with the patient's condition. If possible, 1,000 ml. was administered within 3 hours, as the standard dose. However, some patients received as much as 3,000 ml. and the infusion time was as long as 14 hours per 1,000 ml. in one patient. The average infusion times per unit (500 ml.) of dextran and gelatin were 2.7 hours and 2.5 hours, respectively. The immediate postoperative period was selected for these studies, since major hemorrhagic loss of the plasma expander could not be controlled prior to this time. Nevertheless, many of the patients were still hypotensive and in serious condition at the time of the study.

During the entire period of infusion and for the length of the study, urine was collected from an indwelling catheter. Aliquots for chemical analysis were taken immediately after the infusion and if the volume was sufficient to permit accurate sampling, at 3-, 6-, 12,- 24-, 48-, and 72-hour intervals. Samples were collected from a few patients for periods up to 7 days for each expander. Heparinized blood samples were drawn simultaneously, and additional plasma volume determinations performed, if feasible, immediately post-infusion and at 6-, 24-, and 72-hour intervals thereafter. Intermediate plasma volumes were estimated by interpolation.

Chemical analyses were performed at the forward surgical hospital. Samples that were not analyzed immediately were stored in the frozen state until analysis was feasible. Plasma and urinary dextran levels were determined by the method of Bloom,[3] with only minor modification in technic necessitated by the situation. The procedure, in brief, consisted of alkaline hydrolysis of any protein, precipitation and isolation of macromolecular saccharides, and colorimetric determination of these saccharides with concentrated sulfuric acid and anthrone.

Gelatin determinations in plasma and urine were performed by the measurement of hydroxyproline resulting from acid hydrolysis of the sample, by the method of Neuman and Logan.[11] The method uses p-dimethylamino benzaldehyde for color development. The use of known quantities of gelatin for standards enabled conversion of hydroxyproline levels to gelatin levels. Plasma volume determinations were by a T–1824 dilution procedure, basically that of Gregersen,[7] using three interval measurements to assure complete mixing. Occasionally, mixing appeared incomplete after the third sampling. Such determinations were discarded and values estimated by interpolation or clinical judgment.

Results

The data obtained from the 16 patients receiving dextran and the 10 receiving gelatin are reported on the scattergraphs shown in Figures 1 through 4. Figures 1 and 2 show the rate of disappearance from the plasma and Figures 3 and 4 show the cumulative urinary excretion for dextran and gelatin respectively. The scatter of the individual points is indicative of the variation. As Figures 1 and 2 demonstrate, both expanders remained in the circulation for approximately the same period of time

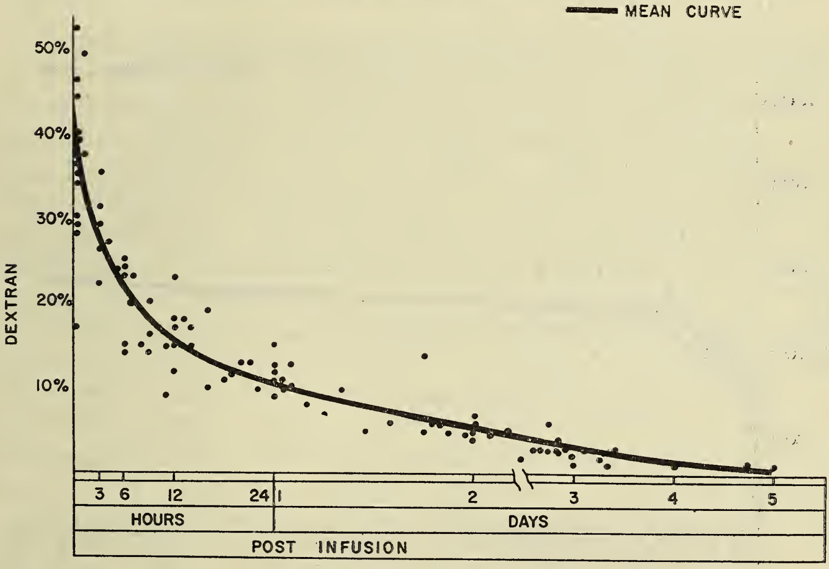

FIGURE 1. Percentage of infused dextran in plasma of 16 combat casualties.

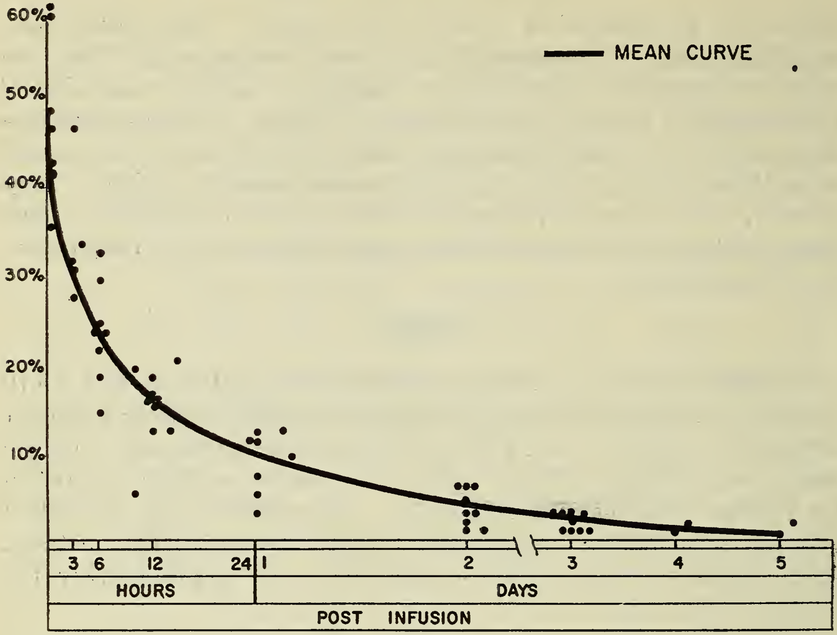

Figure 2. Percentage of infused gelatin in plasma of 10 combat casualties.

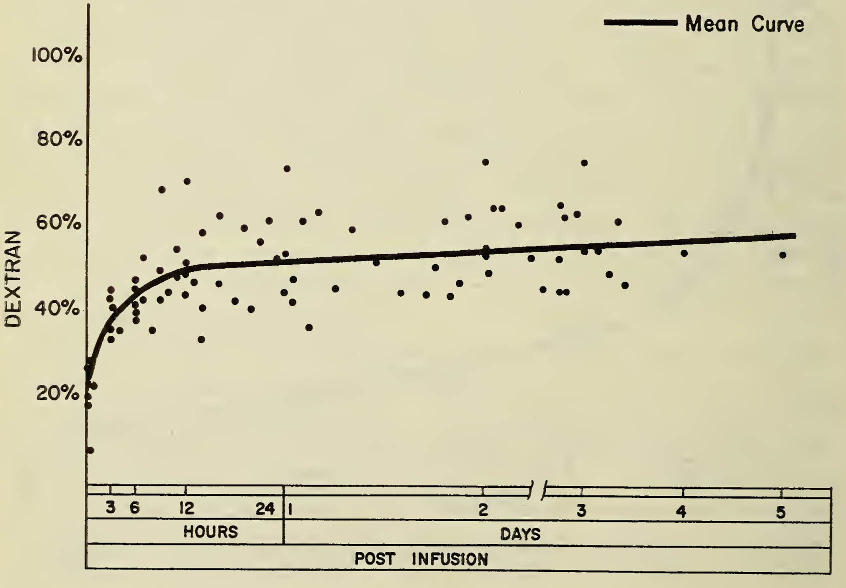

Figure 3. Cumulative percentage of dextran excreted in the urine of 16 combat casualties.

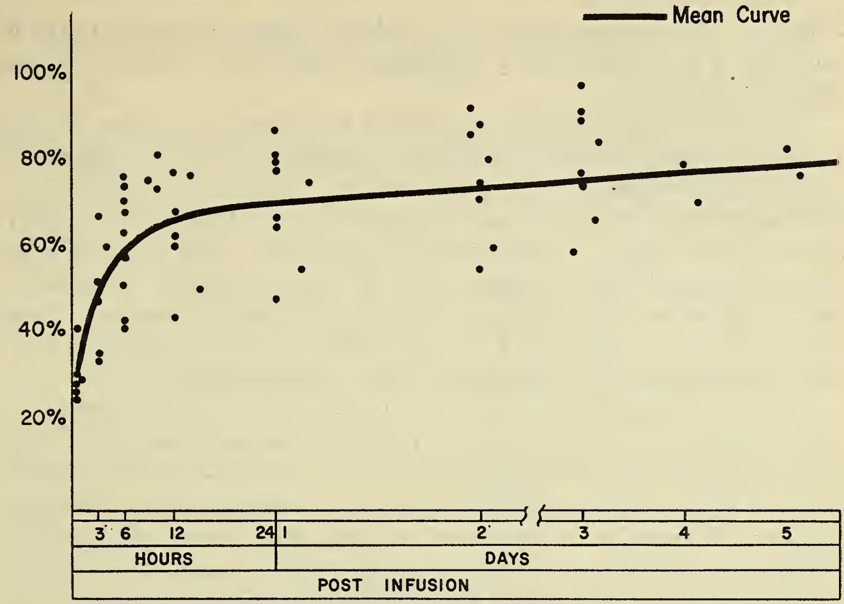

Figure 4. Cumulative percentage of gelatin excreted in the urine of 10 combat casualties.

Six hours after complete infusion an average of only 21 per cent and 23 per cent of dextran and gelatin, respectively, remained. Twelve hours post-infusion an average of only 15 per cent remained for each expander. Subsequent levels fell logarithmically with time to less than 3 per cent at 72 hours post-infusion. This rapid disappearance from the plasma is clearly a function of urinary excretion as indicated by Figures 3 and 4. Six hours post-infusion, an average of 45 per cent and 60 per cent of the infused dextran and gelatin had been excreted in the urine. The amount recovered in the urine continued to reflect the plasma loss until at 72 hours, 58 per cent and 75 per cent had been excreted. It should be noted that the difference in the total quantities excreted need not reflect a true difference in excretion of macromolecular weight compounds, since inherent differences in chemical methodology exist. The method employed for the dextran determinations will determine dextran and some of the polysaccharide intermediary metabolites thereof. However, the method employed for gelatin will detect not only the parent molecule but also the intermediary metabolites, even to the free amino acid stage. Thus, the additional amount of urinary gelatin may reflect the additional metabolic products detected by the chemical procedure. This same consideration should be applied to the interpretation of the different slopes of the linear portions of the urinary excretion curves—Figures

3 and 4. The steeper slope of the delayed gelatin excretion curve is probably a reflection of the additional metabolites detected by the chemical procedure.

Addition of the cumulative excretion and plasma retention at any period of time reveals a significant quantity of either dextran or gelatin unaccounted for by these studies. Six hours post-infusion, this "unaccounted-for" fraction averaged 34 per cent for dextran and 17 per cent for gelatin. Loss through hemorrhage, into extravascular space, by metabolism,[5] storage, and by other excretory pathways [6] may all be factors contributing to this unaccounted-for fraction. This difference in the quantity of unaccountable dextran and gelatin may reflect the difference in specificity of the analytical methods.

The cases heretofore reported have been studied following operation after hemorrhage was controlled. Of additional importance in evaluating the practicality of an expander in the treatment of mass casualties was information regarding circulatory retention prior to surgical therapy. Therefore, a series of 10 casualties were administered dextran at a forward aid station and the plasma concentration measured between 1 and 4 hours later, upon arrival of the patient at a surgical hospital. These patients had no definitive treatment before arrival at the surgical hospital, only routine nonsurgical measures being employed to control hemorrhage.

Upon admission to the surgical hospital, the blood pressure was determined, and a blood sample drawn for chemical analysis. Blood volume determinations were impossible since hemorrhage was not adequately controlled and blood transfusions were needed almost immediately. For the purpose of calculating the percentage of the expander remaining in the circulation, it was necessary to make an estimation of plasma volume based upon clinical judgment, weight of the patients, and knowledge obtained from hundreds of T–1824 plasma volume determinations on other patients. The values used ranged from 2,200 to 2,500 ml., depending upon these conditions.

Table 2 shows the degree of hypotension upon admission to the surgical hospital and the approximate percentage of dextran remaining in the plasma at this time. It was observed that all 10 patients arrived without serious hypotension although many were seriously wounded and required multiple whole blood transfusions before and during operation. It was also observed that from 23 to 42 per cent of the plasma expander remained in the plasma, depending in general upon the time required for evacuation. The rate of disappearance from the circulation appears somewhat greater than in postoperative patients. This difference, however, appears small enough to be explainable by the existing hemorrhage.

Table 2. Plasma Retention of Dextran During Evacuation of Combat Casualties

Time of Evacuation (Hours)	Units of Dextran Administered	Blood Pressure at End of Evacuation	Approximate Per Cent of Plasma Dextran at End of Evacuation
1	1	128/50	41
1	2	100/68	40
1. 5	1	110/50	30
1. 5	1. 6	160/80	42
1. 5	2	90/70	27
1. 5	2	110/58	25
2	1	120/68	32
2	2		32
3. 5	2	150/80	23
4	1	120/80	80

Discussion

Previous investigators have demonstrated the relationship between circulatory retention and molecular size of dextran and gelatin.[4, 9] Therefore, any interpretation of the results of this study must take consideration of these facts. Because of the low molecular weight of both the dextran and gelatin used in this study, prolonged retention could not be anticipated. However, in order to decide if the disappearance rate was faster in the seriously wounded, it is necessary to compare results with a study in normal individuals given expanders with the same molecular distribution. Although such a study is not, to our knowledge, available for dextran, it is available for gelatin. Rousselot,[12] using the same lot of gelatin as employed in our other studies, found that the plasma retention of 10 normal humans averaged 35 per cent 6 hours post-infusion and 12 per cent 24 hours post-infusion. Since their infusion time was only 20 minutes as compared with our 2.5 hours per unit (a lag of approximately 4 hours for 2 units), our retention figures of 23 per cent at 6 hours and 9 per cent at 24 hours are quite comparable. We, therefore, feel that the circulatory retention of gelatin in seriously wounded combat casualties is not significantly different from that found in the normal.

One of the basic limitations to the use of dextran and gelatin for the maintenance of blood volume is their temporary retention. Figures 1 and 2 clearly emphasize this consideration. However, the circulatory retention of both dextran and gelatin was of sufficient duration to permit circulatory support during an evacuation period of several hours. It should be emphasized that the retention studies herein reported are based on rather slow drip infusions—averaging 2.5 hours per 500 ml. Since the infusion of plasma expanders in practice often took place almost continuously during evacuation, the immediate post-infusion retention (approximately 40 per cent) was an index of the degree of expansion upon the arrival of the casualty at the surgical hospital. Successful management of the patient during evacuation was, therefore, possible despite the temporary volume expansion. More prolonged expansion would be desirable for situations involving greater delay before the administration of whole blood and undoubtedly could be furnished by larger molecular fractions.[4, 9] However, the expansion obtained from 42,000 molecular weight dextran and 34,000 molecular weight gelatin was satisfactory for the short evacuation time in Korea.

Conclusion

Plasma retention and urinary excretion of dextran (average molecule size—42,000) and modified fluid gelatin (average molecule size—34,000) have been followed in a total of 26 seriously wounded combat casualties. No significant difference in plasma retention was observed between the two expanders. The retention of both was of short duration, 21 per cent or 23 per cent being retained in the plasma 6 hours post-infusion. This rate did not appear to be significantly different than that in normal humans receiving the same molecular weight fraction (gelatin). The rapid loss of the expander from the plasma was reflected by a rapid urinary excretion. Nevertheless, both expanders, when administered slowly, maintained a circulating concentration capable of sufficient volume expansion to support many casualties for several hours before blood administration.

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Chapter 13

The Fate of Dextran and Modified Fluid Gelatin in Casualties with Renal Insufficiency*

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Captain Yoshio Sako, MC, USAR

Previous studies have demonstrated that much of the dextran or modified fluid gelatin, when infused into the normal subject or the injured soldier,[3] is rapidly excreted in the urine. Cumulative measurement of the urinary excretion, and serial measurements of plasma concentration and volume in the severely injured soldier fail to account for approximately 30 per cent of the infused dextran and 20 per cent of the modified gelatin 24 hours after infusion.[3] (Evidence has been presented that at least part of the dextran is metabolized.)[4, 5, 8]

The treatment of casualties with acute renal insufficiency offered an opportunity to study the fate of these expanders under conditions where urinary excretion would be minimized.

The study was carried out on the Eastern Front in Korea in 1953. Studies were begun at the forward Surgical Hospital and continued following evacuation to the Renal Insufficiency Center, 100 miles to the rear.

Materials and Methods

The dextran used in this study and in the study of the nonoliguric casualties was lot number *250R2*, Commercial Solvents Co. Its average molecular weight was 42,000.[3] Dextran analysis was by the method of Bloom and Wilcox.[2]

The modified fluid gelatin used in this study and the study of the nonoliguric casualties was lot *MFG # 9* of Knox Gelatine Company. Its average molecular weight was 34,000.[3]

Gelatin analysis was by the method of Neuman and Logan (hydroxyproline).[7, 3]

Plasma volume determinations were made by the T–1824 dilution procedure [6] using three interval samples to assure complete mixing.

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*Previously published in *Surgery, Gynecology and Obstetrics 100*:207, 1955.

Observations

Dextran

Dextran was administered to two casualties with renal insufficiency.

Patient No. 12. This Korean soldier, blood type A, was admitted with a perforating wound of the intestine and several penetrating wounds of the extremities. During operation he received 500 ml. of type B blood. A hemolytic reaction with hemoglobinemia and hemoglobinuria resulted. He was immediately given 2,000 ml. of dextran (120 gm.) in an effort to produce a diuresis but his urinary output during the ensuing 24 hours was only 700 ml. This represented a relative oliguria after such an infusion of dextran. The second day his urinary output was 950 ml. and thereafter was 1,600 ml., 2,100 ml., and 3,000 ml. on succeeding days. His blood nonprotein nitrogen concentration rose to 100 mg. per 100 ml. but the patient was never critically ill. He represented a patient with a mild form of renal insufficiency.

Patient No. 17. This American soldier was admitted with severe compound, comminuted fractures of both upper femurs, which resulted from a jeep accident. His blood pressure was imperceptible and rose very slowly during transfusion. After the administration of 10,000 ml. of blood, his pressure was 120 mm. systolic. Operation was not performed. There was no external blood loss. One thousand ml. of dextran was then given intravenously during a 3-hour period. His urinary output averaged approximately 200 ml. per day for 2 weeks after which he diuresed. During the course of the oliguria his blood nonprotein nitrogen rose to 250 mg. per 100 ml. and his rising serum potassium concentration was controlled only by three periods of dialysis on the artificial kidney. This patient had a very severe degree of renal failure.

The retention of dextran in the two patients with renal insufficiency is demonstrated in Figure 1. Sixteen casualties without renal insufficiency, previously given dextran of the same molecular weight, excreted 54 per cent of the administered drug within the first 24 hours. By comparison, Patient No. 12 with a mild renal insufficiency excreted 28 per cent during the first 24 hours and Patient No. 17 with severe renal insufficiency excreted only 6.5 per cent. The excretion during the ensuing 2 or 3 days was minimal. The curve of renal excretion after the first 24 hours paralleled the curve of excretion in the other casualties (Fig. 1).

Thus after 3 days, Patient No. 17 retained almost 90 per cent of the administered dextran and Patient No. 12 approximately 70 per cent. Nevertheless, the dextran disappeared from the plasma as rapidly as in those patients who had the better renal function (Fig. 2). Thus the fraction unaccounted for in plasma and urine of the non-

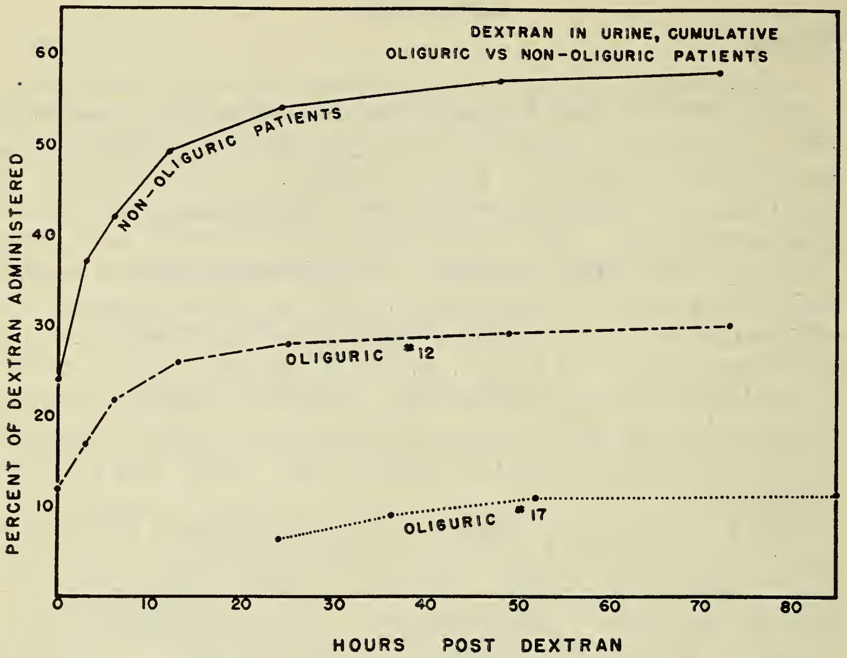

Figure 1. Dextran Excreted in the Urine.

Only 11 per cent of the dextran was excreted in the urine by Patient No. 17.

azotemic patient ranged around 35 per cent of the administered dose, while the unaccounted-for fraction was 60 to 80 per cent in the two azotemic patients (Fig. 3).

Since the wounds were not detectably larger in the azotemic patients, it would seem unlikely that wound exudation accounted for this tremendous loss. The progressive "metabolic loss" after the first 24 hours is essentially the same in the two groups, that is, 1 to 3 per cent per day.

Even after diuresis occurred, dextran did not appear in increasing amounts (Patient No. 12). Equilibration of the dextran between the plasma and extravascular fluid could not be the explanation, as indicated by the following calculations.

If the total body water is assumed to represent approximately 60 per cent of the body weight, the patient's total body water is 40,800 ml. Similarly the extracellular fluid, calculated as 15 per cent of the body weight, is 10,200 ml.

Thus, at 121 hours if the dextran is in equilibrium throughout the total body water, the dextran in this water would be 15.9 grams, leaving an additional 67.7 grams (54.7 per cent of total dose) of dextran metabolized or stored. Similarly, at 121 hours, if the dextran is in equilibrium throughout the extracellular fluid, there would be a

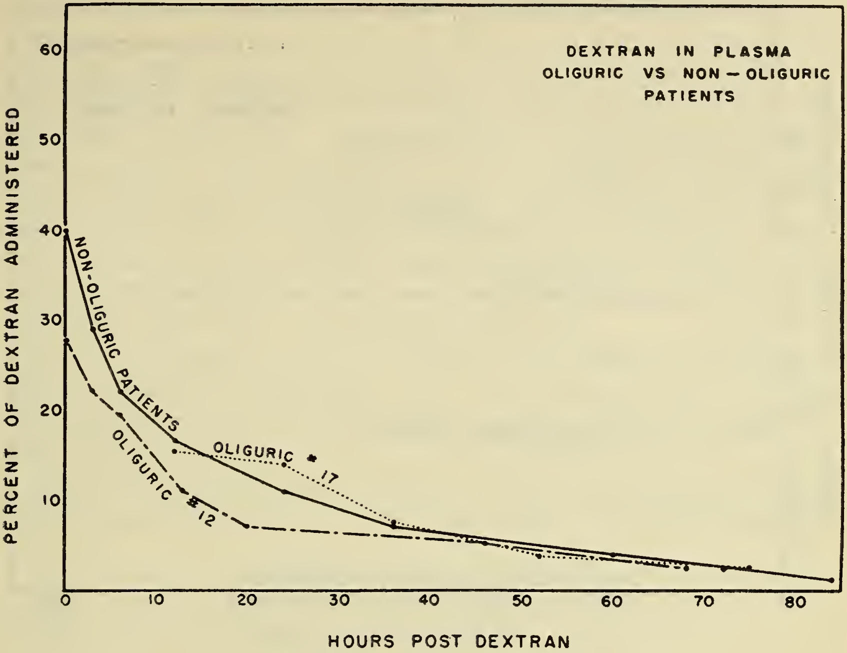

FIGURE 2. Loss of Dextran from Plasma.

Although most of the dextran was retained by the oliguric patients, their plasma concentration was equivalent to that of the nonoliguric patients.

calculated 4 grams in the extracellular fluid, leaving 77.6 grams of the unaccounted-for fraction which had to be metabolized or stored. Equilibration of this fraction with the dextran of the plasma at 121 hours would require the absurd volume of 209,231 ml. (Table 1).

Table 1. Patient No. 12
Weight—68 Kilograms
Dextran Administered—120 Grams

Hours after Infusion	Dextran Unaccounted for in Urine and Plasma		Plasma Dextran Concentration mg./ml.	Calculated Equilibration Volume* ml.
	% of Administered Dose	gm.		
0	60	72. 0	11. 75	6, 127
13	63	75. 6	5. 12	14, 766
49	66	79. 2	2. 40	33, 000
97	68	81. 6	0. 86	94, 888
121	68	81. 6	0. 39	209, 231

*A volume of fluid necessary to contain the "unaccounted-for" dextran if the latter fraction is in equilibrium with the dextran of the plasma.

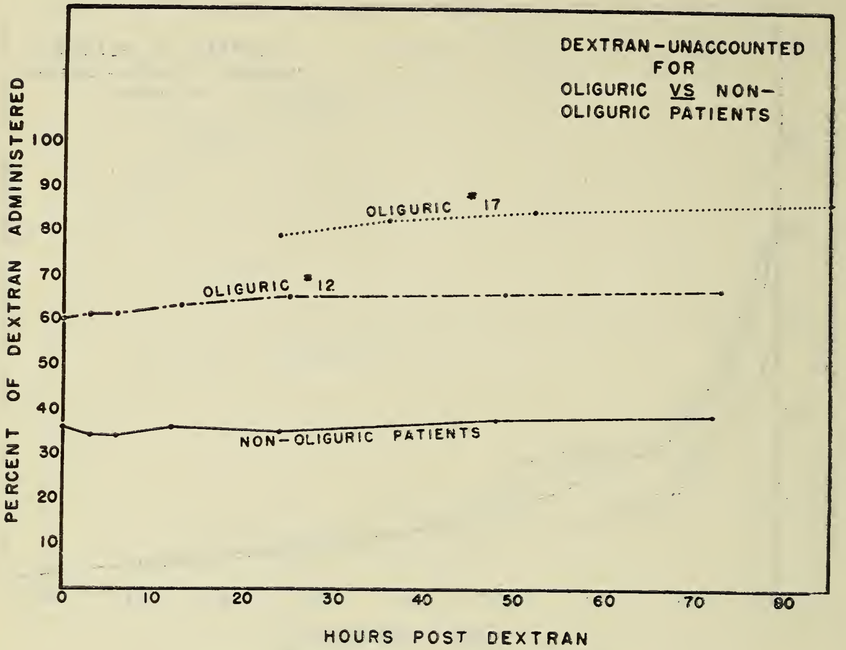

Figure 3. Dextran Deficit.

(Plasma dextran plus urine dextran expressed in terms of dose administered).

Eighty-seven per cent of the dextran could not be accounted for in urine and plasma of Patient No. 17.

An even higher percentage of dextran was unaccounted for in Patient No. 17 (Fig. 3).

These studies extend the observations of Bloom[1] who demonstrated a similar degree of disappearance of dextran from the plasma of rats which had undergone bilateral nephrectomy.

Modified Fluid Gelatin

Two patients with post-traumatic renal insufficiency were studied following the intravenous administration of 3 per cent modified gelatin.

Patient No. 3. This 22-year-old American soldier was wounded on patrol by small arms fire. The injury included perforations of the liver, kidney and colon. He was admitted to the forward Surgical Hospital 4 hours later. Following operation he remained hypotensive although he had received 9,500 ml. of blood. He was then given 2,500 ml. (75 gm.) of modified gelatin. His blood pressure gradually returned to normal. His urinary output during the first 24 hours was 365 ml. but during the second 24 hours fell to 100 ml. His blood nonprotein nitrogen concentration rose to 300 mg. per 100 ml. and his plasma potassium concentration to 7.6 mEq. per liter. He diuresed on the fifth day post-injury but subsequently died of renal abscesses.

Patient No. 4. This 21-year-old Korean soldier was injured by small arms fire. The injuries included perforations of the small intestine and spleen. He was given 2,500 ml. of blood during splenectomy and repair of the bowel. Postoperatively, he was found to have a plasma volume of only 1,590 ml. and to be oliguric. He was then given an infusion of 1,000 ml. (60 gm.) of modified gelatin within a 4-hour period. The anticipated diuresis did not result but he remained relatively oliguric for 12 hours after which he diuresed. This patient, therefore, represented a very mild form of renal insufficiency which may have been on a functional basis only.

These two patients who were treated with gelatin had degrees of renal insufficiency comparable to the two who were given dextran. The disappearance of the gelatin (Figs. 4 and 5) was also comparable to that of the dextran.

Patient No. 3 excreted only 32 per cent, of the administered dose in 24 hours and Patient No. 4 only 35 per cent. In contradistinction

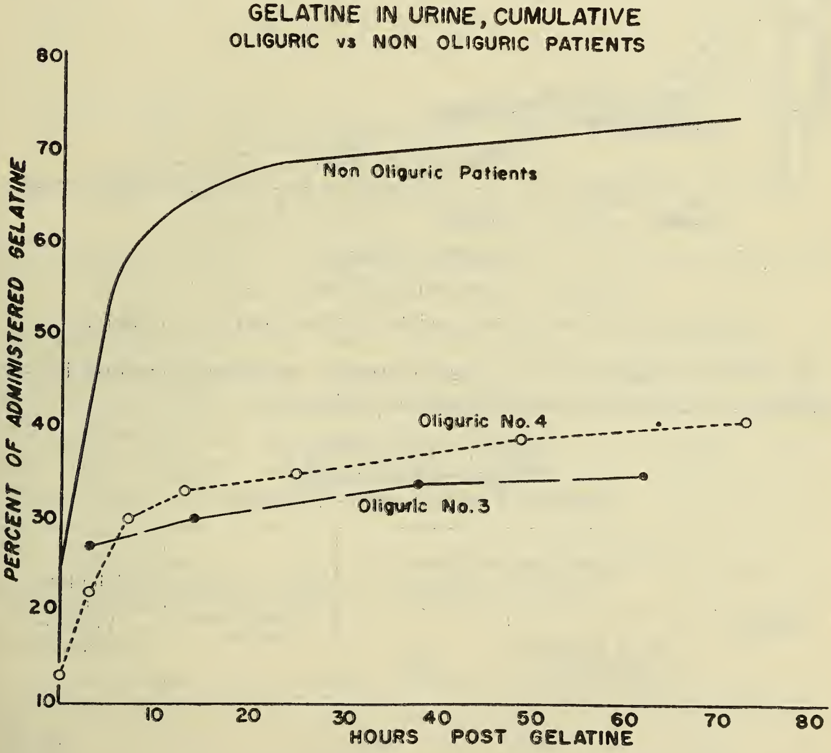

FIGURE 4. Gelatin Excreted in the Urine.

The oliguric patients excreted only half as much gelatin as did the nonoliguric patients.

the nonoliguric casualties excreted during this period an average of 70 per cent. Again, in spite of the marked retention of gelatin by the oliguric patients the total amount of gelatin in the plasma was comparable to that of the nonoliguric patients (Fig. 5). Thus the gelatin fraction unaccounted for in plasma and urine after 24 hours was 20 per cent of the administered dose in the nonoliguric group and approximately 60 per cent in the oliguric patients (Fig. 6).

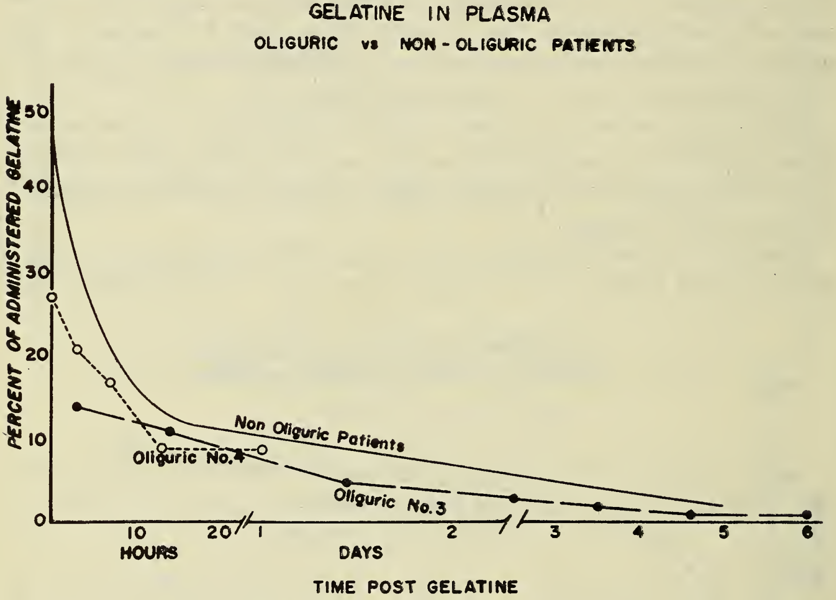

FIGURE 5. Loss of Gelatin from Plasma.
In spite of renal insufficiency, gelatin left the plasma very rapidly.

As with the dextran, the disappearance of gelatin cannot be explained on the basis of equilibration (Table 2).

Table 2. Patient No. 3
Weight—80 Kilograms
Gelatin Administered—75 Grams

Hours after Infusion	Gelatin Unaccounted for in Urine and Plasma		Plasma Gelatin Concentration mg./ml.	Calculated Equilibration Volume ml.
	% of Administered Dose	gm.		
3	59	44. 3	3. 6	12, 250
38	61	45. 8	1. 4	32, 714
124	61	45. 8	0. 2	229, 000

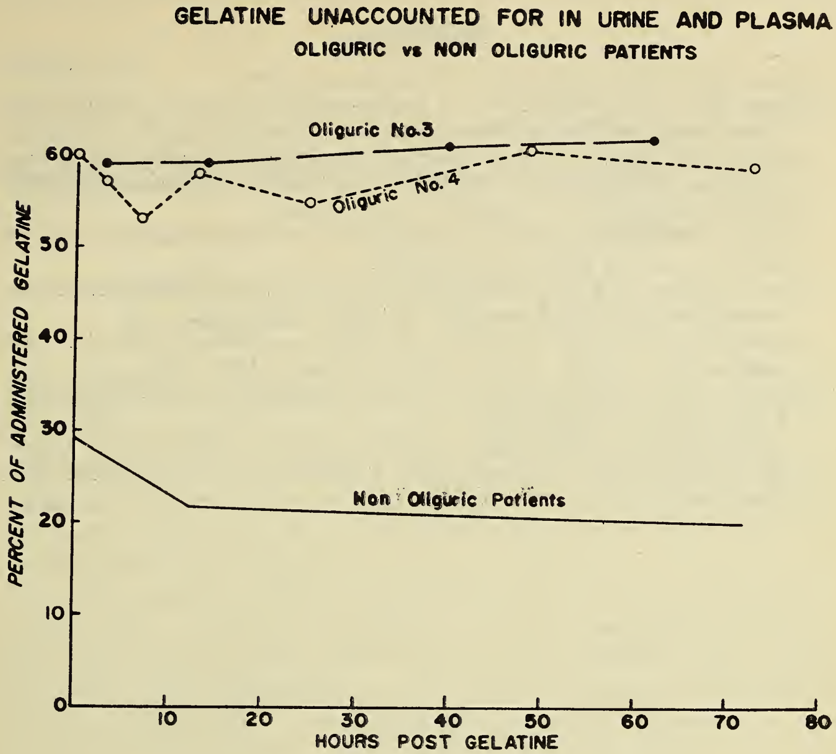

Figure 6. Plasma Gelatin plus Urine Gelatin.
Expressed in Terms of Dose Administered.
Sixty per cent of the gelatin could not be measured in urine and plasma of the oliguric patients.

Calculations as above would indicate that if equilibration was assumed throughout the estimated total body water, 39.8 grams (53.1 per cent of the administered gelatin) was stored or metabolized. If equilibration was assumed throughout the extracellular water, 43.4 grams (57 per cent) was stored or metabolized. Again the theoretical equilibration volumes demonstrated in Table 2 become absurd at 124 hours.

Modified gelatin, therefore, must also be stored or metabolized in large quantities in this type of patient.

Conclusions

1. The disappearance rate of dextran and modified gelatin from the plasma is not entirely dependent upon the rate of urinary excretion.

2. In the patients with acute renal insufficiency of the types observed dextran and modified gelatine appear to be stored or metabolized in large quantities.

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Chapter 14

Clinical Observations on the use of Dextran and Modified Fluid Gelatin in Combat Casualties*

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Captain John M. Howard, MC, USAR
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Immediately after World War II, the search was intensified for some type of macromolecular substance that could be given to maintain plasma volume expansion until whole blood was available. A complete review of the history and status of these plasma volume expanders was reported by Gropper, Raisz and Amspacher[1] in 1952. It appeared that dextran and modified fluid gelatin were safe compounds and effective plasma volume expanders.

In the summer of 1952, Amspacher and Curreri[2] conducted an initial study on the use of dextran in combat casualties in Korea. After using approximately 200 bottles in the treatment of 60 casualties, it was their impression that, although dextran was not a substitute for whole blood, it was a good plasma volume expander for use until blood was available. They found no toxic reactions.

Further study appeared warranted for three basic reasons: (1) blood was seldom available at the most forward medical installations, (2) the incidence of hepatitis following the use of pooled plasma in Korea was almost prohibitive, and (3) experience was needed as a background for the use of blood substitutes in any possible atomic conflict or accident in the future.

With this background, a broad metabolic and clinical investigation was undertaken during 1952–53. During the last 6 months of the study, two infantry divisions used the plasma expanders almost exclusively. Additional experience was gained at the Mobile Army Surgical Hospital supporting these divisions.

As a result of these studies, and based on recommendations of the National Research Council's Subcommittees on Shock and on Sterilization of Whole Blood, pooled plasma was withdrawn from the medical installations in Korea and dextran and human serum albumin were used instead. As a result, during the last 3 months of the study, dextran and albumin were used almost exclusively for resuscitation forward of blood-bank facilities.

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Studies of plasma volume expansion and the plasma retention and urinary excretion of dextran and modified fluid gelatin in the Korean casualties have previously been recorded.[3, 4, 5] It is the purpose of this report to summarize the clinical experiences in the use of 4,000 units (500 cc.) of dextran and 200 units (500 cc.) of gelatin in the anticipation that the experience may prove of value in the management of mass casualties in any possible future disaster.

Dextran

Approximately 4,000 units of dextran were administered to 2,000 casualties. Careful observations were made for the presence of allergic reactions. There was no evidence of urticaria, bronchospasm, or vasomotor instability. Three patients had a pulse rate of 160 per minute and a blood pressure of 160/100 after the infusion of two units of dextran. These reactions seemed out of proportion to the anemia. They were transient and without apparent sequelae. Their etiology was uncertain. Therefore, it must be stated that no toxic reactions, definitely attributable to dextran, were encountered. An increased bleeding tendency or oozing after the administration of dextran was not clinically appreciated although it was not specifically investigated. Many patients with extensive wounds lost blood by oozing into the dressing, but if this was excessive following the administration of dextran, it was overlooked.

Preparation, Shipping and Storage of Dextran*

The dextran was bottled in units of 500 cc. It withstood shipping well and no breakage was reported. Part of the study was carried out during the winter months. Neither freezing nor gelling was a problem as almost all the dextran was administered within a heated bunker or within the hospital. Freezing occurred during transportation without obvious evidence of damage. The dextran flowed freely and battalion surgeons gave as much as 1,500 cc. within 15 or 20 minutes.

A total of 250 units of dextran in plastic bags was administered. The shipping weight per unit of dextran was 1.5 pounds in the bag and 2.5 pounds in the bottle. Only one bag was defective. It appeared that the plastic bag was ideal for use under conditions where dextran was generally used, namely, at the division level. Manual pressure permitted rapid administration. The bag was universally accepted by medical officers in the more forward areas. It could be carried by the company aid man on patrol in pockets of fatigue clothes, thereby permitting plasma volume expansion almost immediately after a soldier was injured.

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*Prepared by the Commercial Solvents Company, Terra Haute, Indiana. The average molecular weight of most of the dextran used in the clinical studies was 42,000 and 48,000, which is less than the average molecular weight of 75,000 prescribed by the National Research Council.

Effectiveness of Dextran as a Resuscitative Agent at the Division Level

Approximately 3,000 units of dextran were administered to 1,500 casualties at the division level. In most areas it was used routinely when support of the blood volume was required. Many of the patients to whom the dextran was administered were severely hypotensive. Throughout the period of study, the average time of evacuation from injury to arrival at the hospital, at least on the Eastern Front, was 3.5 hours. Cooperating battalion surgeons found dextran to be nontoxic, easily administered, undamaged by freezing, and effective in producing prompt increase in blood pressure and urine flow. At the time of admission to the hospital the condition of patients to whom dextran had been given appeared comparable to the condition of those given like amounts of plasma or albumin.

Clinical Observations on Patients Who Received Dextran at the Hospital

Hemorrhage is obviously accompanied by loss of erythrocytes and the oxygen-carrying capacity of the circulation cannot be replaced by dextran. For this basic reason, the quantitative use of plasma volume expanders was limited. It was found, as demonstrated below, that the healthy young adult could usually withstand the loss of approximately 50 per cent of his erythrocytes without serious complications. A comparable loss of total circulating fluid, however, may be fatal unless it is corrected. Dextran proved to be effective in restoring blood volume, in restoring blood pressure and supporting circulation if the loss of erythrocytes had not produced too serious a state of anemia. Many observations on the response of 150 carefully studied battle casualties have supported these facts. During resuscitation, each unit of dextran caused a fall of approximately 5 volumes per cent in the hematocrit. This resulted in part from bleeding and in part from hemodilution by the infused dextran. In general, it was found that a casualty with moderately severe injuries could tolerate 2,000 cc. of dextran prior to blood replacement without immediate serious danger from anemia.

Two thousand cubic centimeters was not an absolute limit in the face of continued hypotension, but beyond this limit the surgeon had to weigh carefully the hazards of acute anemia. A few patients who received more than 2,000 cc. of dextran were maintained without blood for several days after the use of dextran as the sole supportive agent. The hematocrit of these patients fell to 20 to 30 per cent. Very severely injured casualties (those sustaining excessive red cell loss) could not be maintained for more than a few hours without whole blood replacement.

These observations were documented by experience of which the following cases were typical. Knowing from civilian experience that patients could withstand profound but gradually developing anemia, these observations were made in an effort to delineate the limits of dextran therapy against the possible day of atomic disaster when compromises in therapy, if previously considered, might be more judiciously planned.

Patient No. 1. This 22-year-old American soldier, height 61 inches, weight 173 pounds, had been in combat for the previous 8 days. He was wounded at 1130 hours, 12 August 1952, by mortar shell fragments. His wounds included partial amputation of the left foot and approximately 50 small penetrating wounds of both lower extremities. After receiving 100 cc. of albumin, he was evacuated to the forward hospital via helicopter. At the time of arrival at the hospital, 1 hour after injury, his blood pressure was 120/78. He was warm, pale, dry, with fair capillary refilling.

The foot was amputated and many of the wounds were débrided under spinal anesthesia. There was a drop in pressure with the onset of anesthesia. This was controlled by an intravenous drip of neosynephrine and by the rapid administration of dextran. Blood loss from the many sites of débridement was extensive.

By the end of operation 3,400 cc. of dextran had been administered (Fig. 1). His hematocrit had fallen to 12 per cent and he was in respiratory distress for a few minutes. He was immediately given 3,000 cc. of fresh, group-specific blood. His further course was marked by fever (101°—102°) and necrosis of the edges of the amputation stump. Secondary débridement was carried out on the fifth postoperative day under spinal anesthesia. Multiple transfusions of fresh, group-specific blood were given, but in spite of a rising hematocrit and blood volume, his pallor remained quite marked.

This study clearly demonstrated to the observers that if many casualties with injuries of this magnitude were resuscitated with dextran only, serious complications might be encountered. Although this patient's subsequent course was reasonably smooth, and his hepatic, renal and adrenal responses were not unusual,[6, 7] dextran therapy of this magnitude and at this rate is unsafe. Delayed dé-

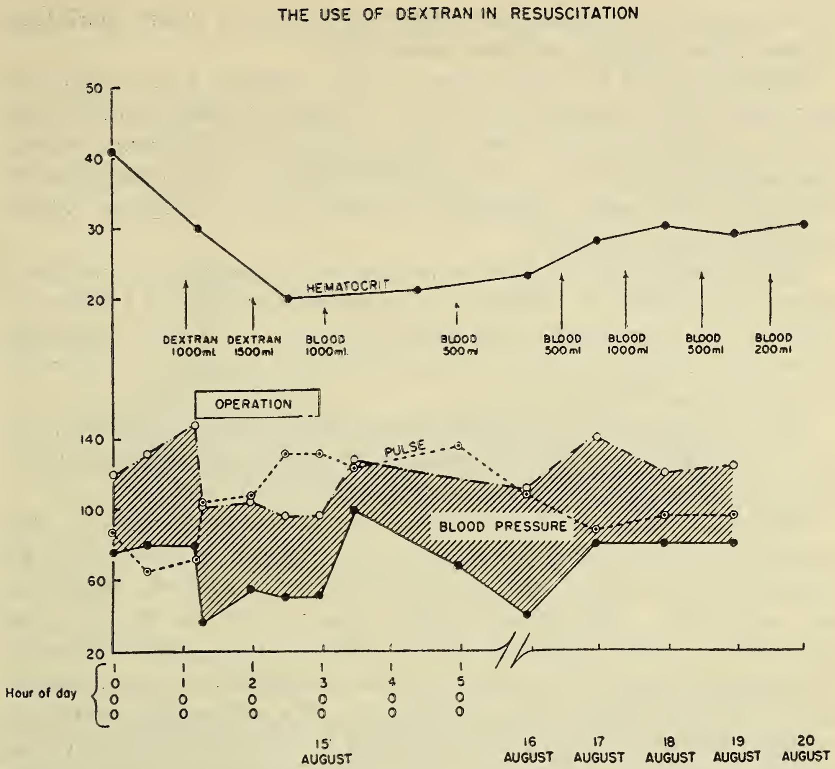

FIGURE 1. Following the administration of 3,400 cc. of dextran, the patient revealed signs of anoxia. Tachycardia was marked; the blood pressure essentially normal. The last fall in blood pressure probably reflected the rapid excretion of dextran. Although the dextran supported the total blood volume, the rapidly falling hematocrit (12 per cent) probably reflected the limiting factor, the total mass of circulating erythrocytes.

bridement would probably prove safer than the use of dextran in this quantity, for this patient demonstrated acute symptoms of anoxia.

Patient No. 2. This 22-year old American soldier, weight 192 pounds, was wounded at 2200 hours, 3 November 1952. He arrived at the hospital via ambulance at 0715 hours the following morning. His injury, from mortar and grenade fragments, included approximately 50 small penetrating wounds of all extremities in addition to fractures of the mandible and one metatarsal.

At the time of admission, his blood pressure was 110/80, pulse rate 100 per minute. He was pale, cool, had slow capillary refilling and a pulse volume of low magnitude. His plasma volume was 3,470 cc. (Evans Blue Dye method), blood volume 6,800 cc. This represented an estimated deficit of 14 per cent in the plasma volume. After 1,000 cc. of dextran, operation was begun (1200 hours) under pentothal, nitrous oxide, oxygen, and ether anesthesia.

Débridement of 30 of the larger wounds required 2 hours and was associated with an uneventful course. A total of 2,000 cc. of dextran had been administered by 2000 hours. At this time his plasma volume was measured as 4,160 cc., blood volume 5,940 cc. Thus his operative blood loss had been replaced by dextran and his plasma volume deficit had been corrected.

The following day his pulse rate rose to 160 per minute, his blood pressure fell to 105/70. A fifth pint of dextran resulted in a fall of his pulse to 130 per minute, his pressure rising to 120/80. Gradually thereafter, the tachycardia decreased although it remained 80 to 110 per minute for 10 days.

Fifteen wounds were closed under local anesthesia on the sixth day and 15 on the tenth day. Healing was progressing satisfactorily at the time of evacuation on his twelfth postoperative day.

This patient tolerated well 2,000 cc. of dextran during surgery. The dextran was given more slowly than to the preceding patient and his hematocrit did not fall below 30 per cent during the period of operation and anesthesia. The following day, however, as the dextran was excreted, a marked tachycardia and slight hypotension developed. This was improved by increasing his blood volume by the administration of the fifth pint of dextran (Fig. 2). His subsequent course, including wound healing, was uneventful. Such a patient with extremity wounds, resuscitated with blood, characteristically demonstrated a progressive fall in hematocrit over the ensuing week. The peaks in the hematocrit on 5 November and 7 November represented the result of the rapid excretion of dextran. Thereafter, continued hemodilution was noted.

Under conditions where compromise in therapy becomes essential, such a patient as this may reasonably be resuscitated with dextran only, but this represents the maximal safe limit of such therapy. Blood is unquestionably to be preferred.

Patient No. 3. This 20-year-old American soldier, weight 178 pounds, 5 feet 9 inches tall, was wounded at 0815 hours, 15 August 1952. The injury, inflicted by a land mine, consisted of a traumatic amputation of the right foot and multiple soft tissue wounds of the left thigh and leg. A tourniquet was immeditely applied and he was given 15 mg. of morphine.

On arrival at the hospital at 0955 hours, his blood pressure was 120/76, pulse rate 76, hematocrit 41 per cent. His skin was cool and pale; capillary refilling was good.

After 1,000 cc. of dextran his blood pressure was 148/82, pulse 84.

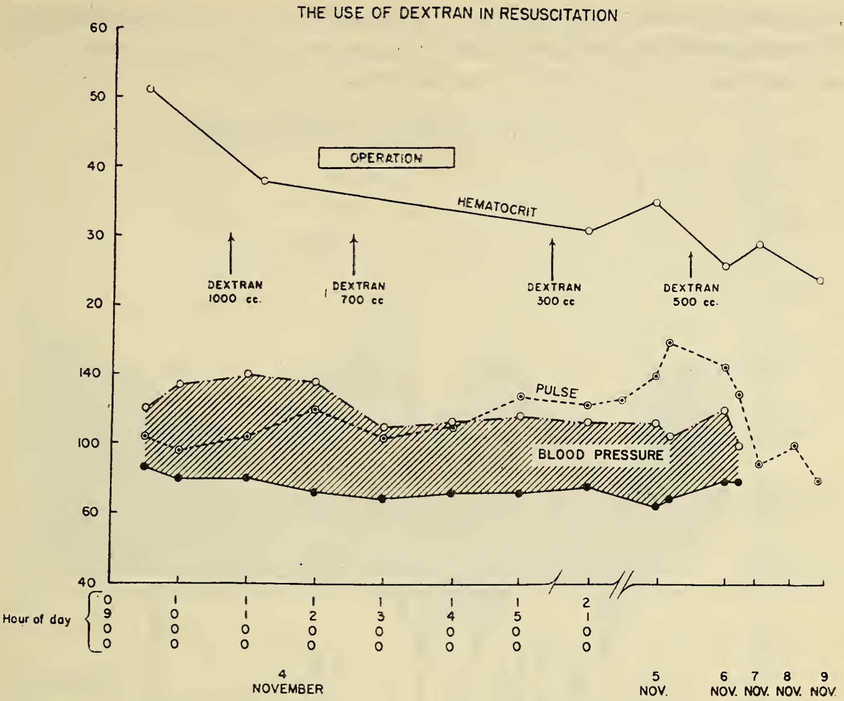

Figure 2. In contradistinction to patient No. 1 (Fig. 1), the hematocrit in this patient did not fall below 30 per cent during the period of the additional insult of anesthesia and débridement.

Operation was then begun (1115 hours) under pentothal, nitrous oxide, oxygen, and ether. With induction, his pressure immediately dropped to 104/38, pulse 104 per minute. Bleeding was rather rapid during the amputation and his pressure dropped momentarily to 65/35, pulse rate 132 per minute. The hypotension was partially controlled by neosynephrine. At this time (1225 hours) he had received 2,500 cc. of dextran and his hematocrit was 20 per cent. As further hemodilution was considered unwise, he was then given 1,000 cc. of fresh blood. At the end of operation (1300 hours) his blood pressure was 96/48, pulse 132, hematocrit 21 per cent. Another 500 cc. of blood was given. His subsequent course was smooth until a transfusion on the fourth day postoperative resulted in a hemolytic reaction.

This man tolerated 2,500 cc. of dextran fairly well. However, it was difficult to maintain his pressure under the combined effects of spinal anesthesia, operative bleeding, and anemia. His subsequent course, as related to the dextran, seemed uneventful. His hepatic, renal and adrenal responses were essentially those seen in patients resuscitated with fresh whole blood.[6,7] The transfusion reaction on the fourth postoperative day was probably unrelated to the dextran therapy. The tachycardia slowly subsided as repeated transfusions resulted in an increase in the circulating red cell mass (Fig. 3).

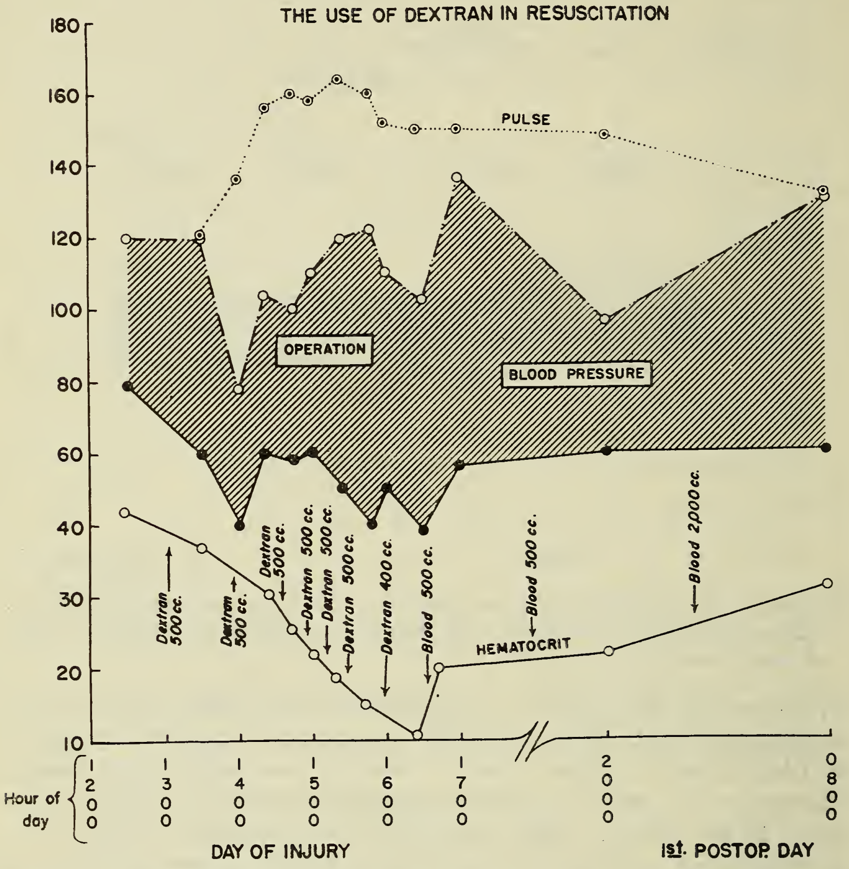

Figure 3. Each 500 cc. unit of dextran resulted in a fall in the hematocrit of five volumes per cent.

Had blood not been immediately available, interruption of the operation might have been necessary.

Patient No. 4. The following report is a typical example of a casualty who was resuscitated with dextran only.

A 21-year-old American private was injured on 7 April 1953, at 2100 hours, when a 50-caliber machine gun missile perforated his left thigh, causing an open comminuted fracture of the left femur. Three hours later, he arrived at the surgical hospital with a blood pressure of 138/80, pulse 90, and a good dorsalis pedis pulse. His hematocrit was 44 per cent. He was given 500 cc. of dextran prior to operation. He lost approximately 2,000 cc. of blood during the operative procedure. A tremendous amount of tissue had been destroyed. It was necessary to explore the popliteal area and to do an extensive débridement with wide excisions on both sides of the lower extremity. He was given three additional units of dextran during the operative procedure. At one time, his blood pressure fell to 80/60 and his pulse rate rose to 120. However, after the administration of the fourth unit of dextran, his blood pressure returned to normal. A few hours after operation, his hematocrit was 27.5 per cent, his urine output 60 cc. per hour. Twelve hours after operation his hematocrit was 28 per cent; on the second postoperative day it was 25 per cent. He appeared to be well except that he was pale and listless. His urinary output remained excellent. He received 1,000 cc. of blood on the third and again on the fourth postoperative day. His hematocrit rose to 39 per cent and he was in good condition at the time of evacuation.

This patient demonstrates that a large amount of tissue destruction together with the loss of approximately 2 liters of blood may be tolerated by a young man when supported with dextran. Although his hematocrit fell to a rather low level, he experienced no serious deleterious effects.

Comment

Except in a few instances, whole blood was preferred in the management of most patients at the hospital level. Dextran was preferred as the colloid in the treatment of burns. Most patients with partial-thickness burns received chiefly dextran and very little blood. In the more extensive deep burns, the colloid requirements were usually fulfilled with a ratio of 1 unit of dextran to 1 unit of blood.

Many patients who had abdominal wounds and required prolonged intra-abdominal operative procedures showed a rising hematocrit. The exact cause of this hemoconcentration is unknown, but it is believed to be a loss of fluid into lumen and wall of the gastrointestinal tract and into the peritoneal cavity. During operative procedures on massive wounds of the abdomen, it was the experience of forward surgeons that this hemoconcentration could be corrected by using from 1 to 3 units of dextran in addition to blood.

Ratio of Dextran to Blood

During the last few months of the Korean conflict, 35 casualties were studied who received 1,000 cc. or more of dextran in addition to blood. This was part of a clinical investigation in which dextran and blood were given in varying proportions in order to find a safe and practical ratio in the event that unlimited quantities of whole blood were not available. These casualites had wounds of various types, abdominal, abdominal-extremity, thoraco-abdominal, chest and extremity. All the patients did well. In a few instances it was necessary to give blood on the day following operation either because of a low hematocrit or because of a rapid pulse rate.

Table 1 outlines the maximum amount of dextran given to the patients in each category. Several patients were observed who had a blood volume deficiency of 1,000 to 1,500 cc.; these patients were completely resuscitated using only dextran.

Table 1. Maximum Dextran Given in Various Categories

Ratio of Dextran to Blood	Total Colloid First 24 Hours	Total Dextran
1:1	4,500 cc.	2,500 cc.
1:2	6,500 cc.	2,500 cc.
1:3	11,000 cc.	3,000 cc.
1:4	14,000 cc.	3,000 cc.

From observations on these patients, it has been possible to outline a ratio of plasma expander to blood that may be given without causing dangerous anemia (Table 2). This may be used as a compromise when the supply of blood is limited. The patient's postoperative hematocrit and pulse rate serve as indicators for the need of additional blood.

Table 2. Acceptable Ratio of Dextran to Blood

Resuscitative Fluids Required	Ratio
1,000–1,500 cc.	Dextran alone
1,500–4,000 cc.	1 dextran : 1 blood
4,000–7,000 cc	1 dextran : 2 blood
Over 7,000 cc.	Maximum dextran 2,500 cc. : Remainder blood

Modified Fluid Gelatin

Two hundred units (500 cc.) of modified fluid gelatin* were given to casualties. About one-half of this amount was given in the division area and the remainder in the surgical hospital. There was no evidence of toxicity and the gelatin flowed freely. Observations by medical officers in the division area revealed that gelatin was a clinically effective solution for supportive therapy until the patient reached an installation where blood was available. The usual quantity of gelatin administered was 1,000 or 1,500 cc.; however, some patients received 3,000 cc. On storage, the gelatin did not change color over a period of 8 months. No data were available to determine whether or not freezing had any effect on the gelatin solution. It appeared that, under the conditions in which gelatin was used, it was an effective plasma volume expander; however, it must be pointed out that the average period of evacuation was 3.5 hours. Gelatin in a small series of patients seemed to support the circulation well for this period of time.

Discussion

These experiences extend those of Amspacher and Curreri,[2] who pointed out that battle casualties having mild to moderate blood loss can be treated satisfactorily using only dextran, while those having more severe blood loss require whole blood. By administering dextran, many of the severely wounded casualties can be maintained during first aid and transportation to the hospital. Haynes and DeBakey [8] demonstrated that patients who had lost about 20 per cent of their blood volume could be treated successfully with saline and dextran.

Effective early resuscitation was achieved by dextran alone in patients with moderate shock or with blood volume deficiencies ranging from 20 to 30 per cent, whereas dextran and blood were required in patients who lost more than 35 per cent of their blood volume. We are in general agreement with their conclusion, namely, that a hematocrit depressed by 25 per cent through administration of dextran probably represents the approximate lower limits of a safe level of diminished circulating red cell mass compatible with effective resuscitation.

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*Modified fluid gelatin in this study was 3 per cent in 0.7 per cent sodium chloride, Lot No. MFG–9, manufactured by the Research Department of the Charles D. Knox Gelatine Company, Inc., Camden, New Jersey, average molecular weight, 34,000.

Summary

Observations were made on the administration of 4,000 bottles of dextran to 2,000 casualties during the latter part of the Korean conflict. No toxic reactions were seen. A bleeding tendency following the administration of dextran, although not investigated, was not noted. This plasma volume expander proved to be most satisfactory. Many forward surgeons felt that it was superior as an emergency solution to plasma or albumin.

Patients who required 1,500 cc. or less of resuscitative fluids could be satisfactorily restored with dextran alone. An acceptable ratio of dextran to blood was established for use when unlimited quantities of blood were not available.

Observations were made on the administration of 200 units of modified fluid gelatin. The solution was nontoxic and did not gel. Although the molecular weight was low (average 34,000), the period of evacuation was only 3.5 hours and the circulation was supported for the required period.

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Chapter 15

A Study of the Histological Localization of Dextran in Tissues of Korean Battle Casualties

Captain Austin L. Vickery, MC, USA

For several years there has been mounting interest and investigation in the field of synthetic plasma expanders. Dextran has been amongst the foremost of these substances under active experimental study and clinical application. There have now been many reports in the literature attesting to the efficacy of dextran as a relatively short-term blood volume expander.[1–6] The fate of dextran after it has been infused has been carefully investigated by many methods. It has been shown that 25 to 50 per cent is lost in the urine during the first 24 hours,[5, 8, 12, 13, 15] and the presence of dextran has actually been demonstrated in kidney tissues of animals that had received it.[11, 14] Other investigations have demonstrated that some of the injected dextran is actively metabolized as a carbohydrate.[7, 10, 16, 17] Still other work indicates that some is stored for variable periods of time in the tissues;[9, 19, 20] tissue changes noted after dextran administration have been attributed to the effects of this material.[6, 22-24] Most of these observations were made in animals that received large and repeated doses of dextran, but a few autopsy reports of humans who had received dextran described similar tissue changes, especially in the kidneys.[6] Problems presented themselves concerning the nature of these changes and whether or not they were indicative of damage.

In 1952, a trial use of dextran in Korean battle casualties was undertaken by The Surgeon General's Office. Sixty-seven wounded soldiers in forward areas of the war zone received the substance and the results indicated a satisfactory expansion of the plasma volume. Further limited use of dextran in Korea under the aegis of the Surgical Research Team was approved and liaison with the Pathology Section of the 406th Medical General Laboratory was established for histopathological study of submitted tissues from such patients.

During the initial phase of this tissue study, three autopsies were studied of patients who had received dextran following battle wounds (406 MGL Nos. J–2836, J–2837 and J–2838). Two of these patients had received three units of dextran and one had five units. All three died of their severe wounds within relatively short times after wounding—7 hours, 11 hours and 28 hours. The tissues were fixed in the usual 10 per cent formalin at the 8055th MASH and then forwarded to the 406th Medical General Laboratory. On initial histological examination of this material, no specific changes were observed referable to dextran. However, on reviewing the kidney sections, the tubular changes of epithelial swelling, granularity and vacuolization were recognized to some degree in all three patients. It was decided to apply the recently developed histochemical technic for the actual visualization of dextran in tissues, reported by Mowry, Longley and Millican [21] in 1952; later improvements in the method were also adopted.[20, 25] The basic feature of this development was recognition of the high solubility rate of dextran in aqueous solutions. By fixing tissues in absolute alcohol, processing without aqueous contact and then staining with the periodic acid-Schiff method for polysaccharides, these investigators were successful in staining dextran in tissue preparations.

In order to gain experience with this new technic, to verify the published data and to have histological material as a baseline for further studies on human autopsy material, a series of rats were given intravenous infusions of dextran.[14] These studies confirmed the success of the published technic to delineate what is interpreted as dextran within tissues. Accordingly, the method was adopted for work on autopsy tissues of battle casualties who had received dextran.

From October 1952, until May 1953, a special series of 15 autopsies of patients who had received dextran was performed in Korea. All but one of these were done by Lieutenant Joseph G. Strawitz, MC, at a forward Surgical Hospital in conjunction with the Surgical Research Team's over-all project on the use of plasma expanders in the wounded soldier. Particular efforts were made to perform the postmortem examinations at short intervals following death. Representative tissue blocks were fixed in absolute alcohol in addition to routine fixatives. These were sent to the 406th Medical General Laboratory in Tokyo. The alcohol-fixed material was processed and stained according to the modified Schiff technic of Mowry *et al.*[20]

The basis for the staining of polysaccharides in tissue with the Schiff method is that of a liberation of aldehyde groups (by oxidation of 1, 2 glycol linkages with periodic acid) and then a demonstration of free insoluble aldehyde groups by a specific aldehyde reagent (Schiff's reagent-fuchsin-sulfurous acid). The saccharides in tissues thus treated will stain rose-red to reddish-purple. Obviously this stain is not specific for dextran, for the PAS method colors many natural tissue carbohydrates. The element of confusion between the identity of these positively stained substances and dextran-related materials is largely obviated by the comparison of the tissue section with a consecutive serial control section, stained simultaneously in the same manner but having been exposed to water prior to staining.

The dextran deposits, being highly soluble in water, are absent in the control section. The natural tissue saccharides (i. e., basement membranes, hyaline, colloid, mucin and glycogen) are not completely soluble in either water or alcohol and may appear stained in both sections. Consequently, it is necessary to compare the alcoholic-PAS-stained sections with corresponding aqueous controls, to be certain that what is interpreted as dextran in the former is absent (dissolved out) in the latter.

Before referring to the autopsy findings in this group of battle casualties, some of the aspects and problems relative to the histological identification of dextran should be mentioned. When material identified with dextran was seen in tissues, in the majority of instances, it appeared as discrete purplish-red granules of variable size and at times almost black. When large concentrations were present, the granularity was not observed but instead solid aggregates of very dark, reddish-black, homogeneous material were noted, as in the renal tubular lumina. At other times, particularly within liver and kidney cells, the entire cytoplasm presented a rose-red stain without actual granular aggregates. As with other histochemical procedures, varying degrees of success were sometimes encountered in a uniform employment of the stain by tissues which, at times, defied a rational explanation, particularly in identical sections of the same tissue. However, this difficulty was not in the order of seeing "dextran-stained material" as an artefact but rather a tendency for the dextran material sometimes to accept the stain in one area and not in another where there was no apparent reason for its also not being demonstrable. This patchy staining of dextran-containing tissues was likewise observed in the experimental rats [14] where conditions for prompt fixation, etc., were ideal.

Observations

With the utilization of the noted histochemical technic the following general observations were made in the histological evaluation of dextran in 15 autopsies of severely wounded patients. It should be kept in mind, in the evaluation of these observations, that this series of patients represents a specialized group. The average time interval from the wound episode until death was about 39 hours, and the average time from the start of the last dextran infusion until death was approximately 17½ hours.* However, as noted in Table 1, there were 12 patients whose last infusion was in progress within 12 hours of death. These figures indicate the short temporal range of the study and suggest appropriate considerations in the interpretation of the observations.

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*This average does not include Cases 5, 10 and 14, in which the infusions were given over prolonged periods.

Table 1. Data on Dextran Infusion after Wounding

Case Number	Autopsy Number	Time from Wound Episode to Death (Hours)	Time from Start of Last Dextran Infusion to Death (Hours)	Total Amount Dextran Infused (ml.)	Wound Site	Histological Grade of Dextran in Kidneys	Shock Status
1	J–3198	16½	6	1, 000	Head	4	None
2	J–3199	32½	4½	2, 000	Multiple	5	24 hours before death
3	J–3200	69½	65	1, 000	Extremities	2	Entire course
4	J–3315	40½	4	1, 500	Abdomen and Arm	5	During last 17 hours
5	J–3426	50	*47	4, 500	Burns	2	None
6	J–3430	9	6	1, 500	Head	5	During last few hours
7	J–3434	6½	6	1, 500	Extremities	4	Entire course
8	J–3548	6	1¼	1, 500	Head and Hands	1	Entire course
9	J–3694	¾	¼	500	Head	0	(Died within hour of wound)
10	J–3760	17	*11½	2, 000	Abdomen	3	During last few hours
11	J–3761	4½	4	500	Multiple	2	Died of hemorrhagic shock during operation
12	J–3793	106½	93½	1, 500	Multiple	3	Intermittent entire course
13	J–3858	17	13	1, 300	Chest	0	Terminal only
14	J–3859	42	*20	7, 000	Multiple	5	During 12-hour period postop. None last 20 hours.
15	J–3860	167	5	1, 500	Abdomen	4	Terminal 8 hours (approx.)

*Infusion given continuously until death in Cases 10 and 14, and until 5 hours before death in Case 5.

Histological Grading of Renal Dextran Content:

0—None.
1—Blood vessels only.
2—Patchy, minimal.
3—Patchy, moderate.
4—Diffuse, moderate.
5—Diffuse, marked.

Kidney. Dextran deposits were seen more consistently in the kidney than in any other organ studied. Likewise, it was seen to appear in both blood vessels and parenchyma with relative rapidity. In patients receiving large amounts within a matter of a few hours prior to death, the microscopic picture was a dramatic one. The entire section displayed a deep red mahogany color, contrasting sharply with the light pinkish-red of the aqueous control section. Microscopically, the tubules contained large masses of dark positive-staining material within their lumens, often completely filling the tubule (Figs. 1 and 2). These heavy aggregates of material were most common in the lower nephron and the collecting tubules. The tubular cells likewise showed a staining affinity, and this was most interesting in the proximal convoluted tubules. Here, aggregates of discrete, dextran-staining granules were seen within the cytoplasm of the cells, usually unassociated with intraluminal material (Figs. 3, 4, 5, and 6). This observation was likewise made in the rat experiments (Figs. 7 and 8), corroborating the published data of Mowry *et al.* in mice [20] and is suggestive of tubular absorption or metabolism of dextran. The periglomerular spaces likewise contained granules or small clumps of the stained material.

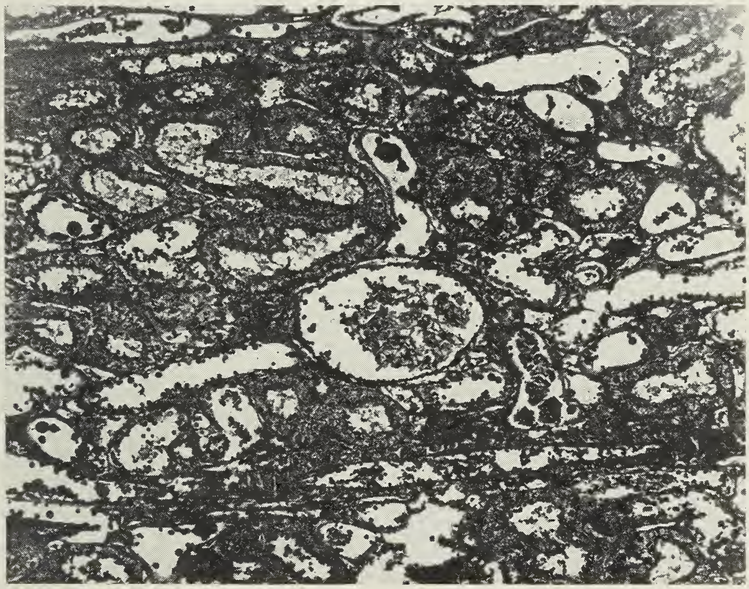

FIGURE 1 (Case #2, Autopsy #J–3199). Kidney section of a soldier who died 32 hours after wounding. He received a total of 2,000 ml. of dextran during the terminal 10 hours of life with the last 1,000 ml. starting 4½ hours prior to death. In addition to the many aggregates of dextran in the tubular and glomerular space, the tubular cells show a marked staining affinity.

Periodic Acid Schiff (Mowry) X 120

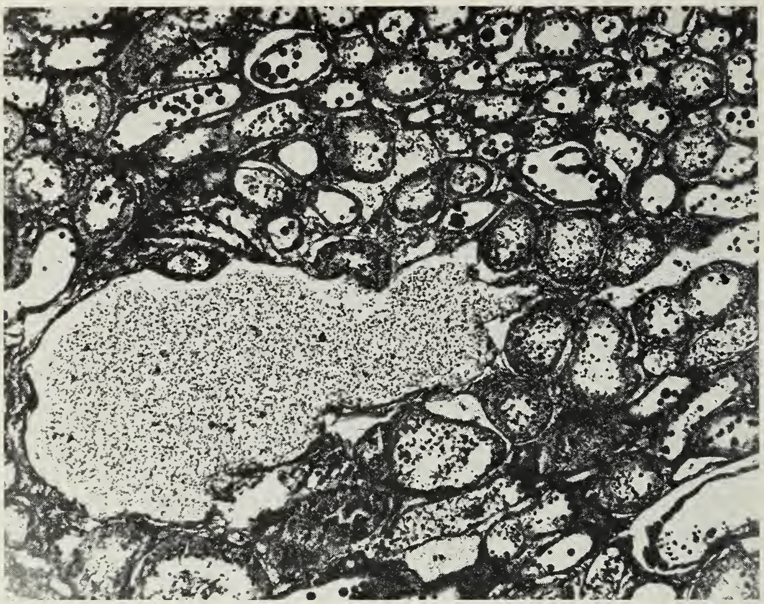

FIGURE 2 (Case #2, Autopsy #J–3199). Another renal section of the same case illustrated in Figure 1. The tubular intraluminal and intracellular localization of the dextran is clearly shown. Note the large vein containing a dense concentration of dextran granules.

Periodic Acid Schiff (Mowry) X 120

In patients who received less dextran and/or at relatively long intervals prior to death, the material had a tendency to be distributed in a patchy or helter-skelter fashion in the kidney with a tendency to localize in isolated peripheral portions of the sections, principally in the convoluted tubules. This heterogeneous distribution, which was seen in other tissues as well, has seemed more likely to be an inherent and somewhat unpredictable feature of the fixation or staining technic than an accurate quantitative reflection of tissue dextran content. However, there appeared to be some degree of correlation between the amount of dextran administered, the time interval until death and the quantities seen in the microscopic sections. As noted in Table 1, an attempt was made to grade the relative amounts of dextran-staining material seen in the kidneys as a relatively crude index for rough correlative purposes with several other variables.

There was no sign of tissue damage, reaction or inflammatory cellular response noted in any of the kidney sections which could be related to the dextran. This was also true for the rat tissues, including those with multiple injections.

The routine H and E kidney sections showed the previously referred to tubular changes of cellular swelling: cytoplasmic vacuolization and

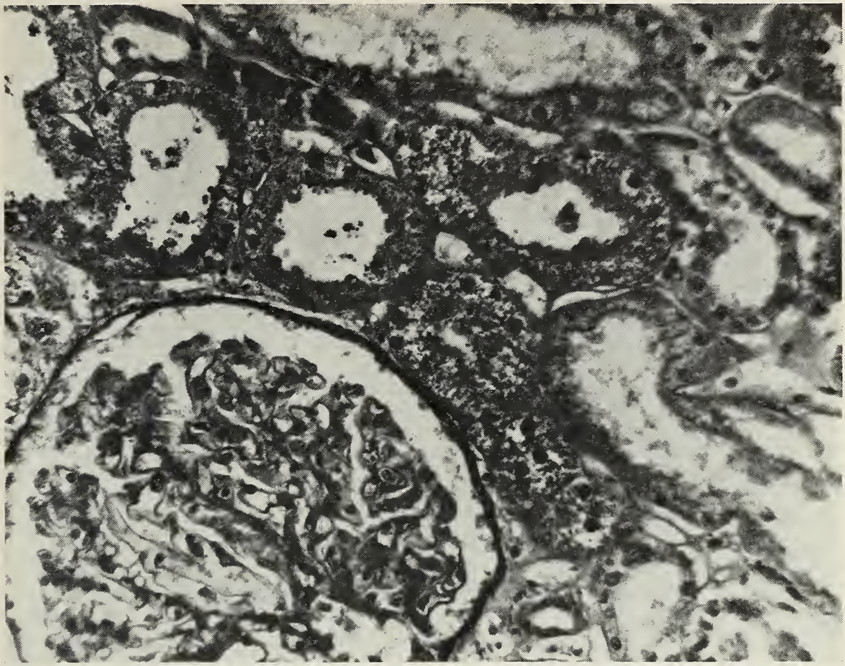

FIGURE 3 (Case #12, Autopsy #J–3793). Dextran granules within the cytoplasm of convoluted tubular cells, presenting a finely stippled appearance. This battle casualty received his last dextran infusion almost 4 days prior to death. The postoperative course was complicated by oliguria (lower nephron nephrosis) and intermittent hypotension.

Periodic Acid Schiff (Mowry) X 240

granularity and intraluminal, amorphous, eosinophilic material (Fig. 9). These findings seemed largely restricted to the convoluted portions of the nephron and, in particular, to the proximal segments where the brush border of the epithelium was often clearly defined. In some instances, the tubular epithelial swelling was quite striking, serving to delimit sharply the convoluted tubules from the adjacent parenchyma (Fig. 10). Efforts to correlate the histological degree of tubular cell swelling with the quantity of dextran administered and the time intervals involved were inconclusive as to a quantitative relationship. However, a rough direct relationship did exist between the amount of dextran seen in the kidney tissue and the amount of tubular swelling. The fact that tubular changes were recognized in all cases, representing a rather wide range of post-infusion intervals and dextran amounts, suggests that these alterations are readily produced and tend to disappear slowly. In none of these cases was there evidence of any degenerative sequences associated with this "nephrotic" picture.

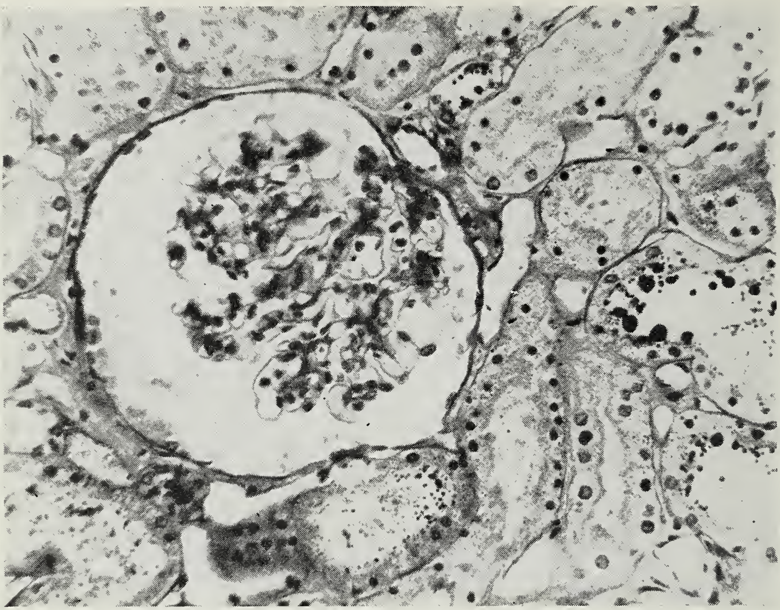

FIGURE 4 (Case #11, Autopsy #J–3761). Kidney section from a soldier who received 500 ml. of dextran at the battalion aid station 30 minutes following multiple severe wounds. He died 4 hours later. Note the dextran aggregates and granules scattered about the tubular parenchyma both within the tubules and the cells. Periodic Acid Schiff (Mowry) X 240

Spleen. Dextran deposits have been described in the splenic reticuloendothelial cells of mice within short intervals following infusions.[20] In the series of rats studied at our laboratory similar evidence was obtained but the most definite identifications were made following multiple and prolonged periods of infusions. The photomicrograph (Fig. 12) is of such a spleen showing the intracellular dextran material circumferentially arranged around Malpighian corpuscles. No associated tissue changes were observed. It was, however, difficult to be certain about the demonstration of minute phagocytosed quantities in the early post-infusion periods. This was likewise true for the human autopsies. On first examination, no dextran-like material was identified but subsequent studies were suggestive of minimal focal phagocytosis; in no case were these deposits unequivocal. There was no recognizable evidence of any tissue reaction in the human spleen.

Liver. The evaluation of dextran within the liver is complicated by the natural presence of glycogen which, being insoluble in both alcohol and aqueous periodic acid-Schiff preparations, appears in both slides.

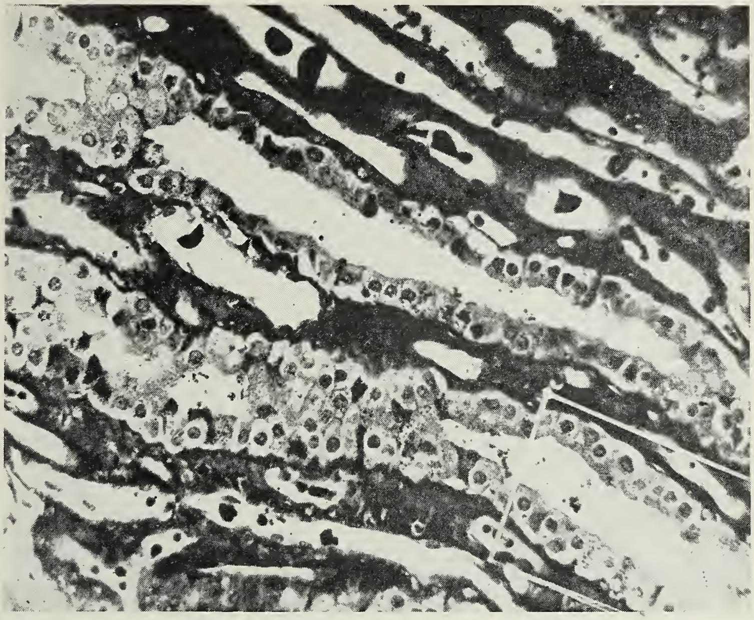

FIGURE 5 (Case #4, Autopsy #J–3315). This longitudinal view of renal tubules shows a rather diffuse sprinkling of dextran granules within the cellular cytoplasm. The cells also appear slightly swollen. This patient received extensive wounds and developed renal insufficiency. He died 41 hours after wounding. A Total of 1,500 ml. of dextran was administered; 500 ml. was given at the battalion aid station and the final 1,000 ml. was infused 4 hours before death.

Periodic Acid Schiff (Mowry) X 240

The dextran-staining material, however, is dissolved out in the aqueous control PAS section, and by careful comparison of both sections its presence can be detected. This was often quite difficult, particularly when the liver cells were laden with glycogen. Discrete phagocytosed granules of dextran-staining substance were also noted within occasional Kupffer cells of two patients with long survival periods between infusions and death. Similar localizations were seen in the rat studies where they were consistently noted in the animals receiving multiple injections over prolonged periods.

Lungs. The lungs of the autopsy cases presented a rather varied picture of dextran identification. The most common finding was that of aggregates of granules within the blood vessels and within alveolar capillaries. There appeared to be a direct relationship between the amount deposited and short intervals between dextran infusion and death. In several of the "short-interval" cases, a few particles were seen in the intra-alveolar spaces, sometimes intermixed with edema fluid (Figs. 13 and 14).

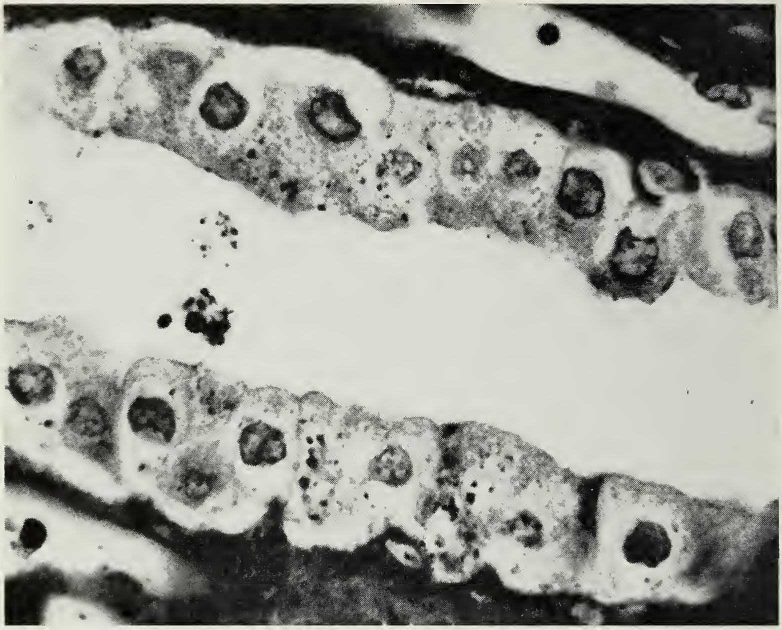

Figure 6 (Case #4, Autopsy #J–3315). This is a higher magnification of the bracketed zone of Figure 5. The intracellular dextran granules and the cellular swelling are well illustrated.

Periodic Acid Schiff (Mowry) X 820

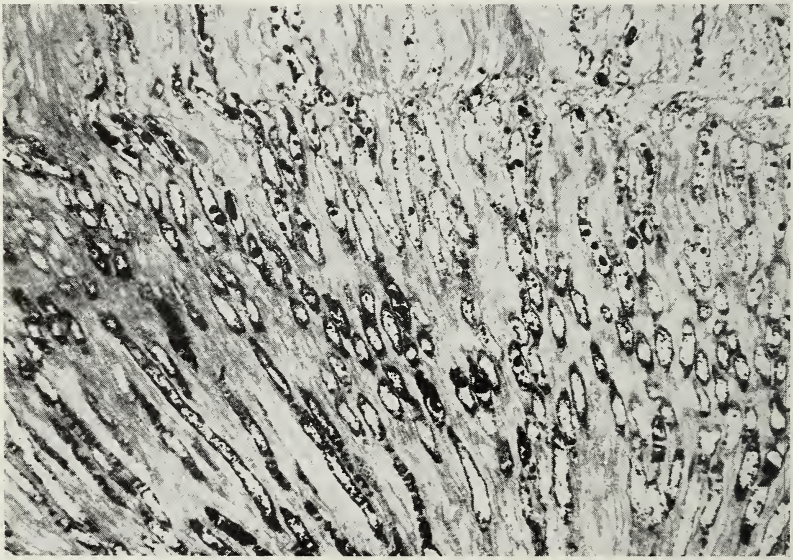

Figure 7 (Rat #M–6627). Low-power view of the medullary portion of a rat kidney 1 hour following a 1 ml. intravenous infusion of dextran. Note the intense tubular concentration of the dark-staining dextran.

Periodic Acid Schiff (Mowry) X 46

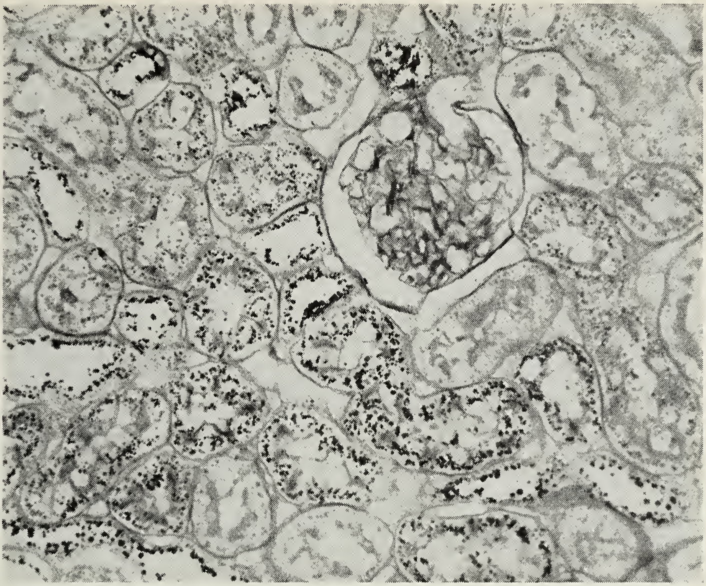

FIGURE 8 (Rat #6627). Kidney section of a rat sacrificed 1 hour following a single 1 ml. intravenous infusion of dextran (see also Figure 7). The rapid appearance of dextran granules, not only in the distal tubular spaces but within the proximal convoluted cells, is well illustrated.

Periodic Acid Schiff (Mowry) X 230

Pancreas. The pancreatic parenchymal cells did not show any intracellular dextran-staining material. In a few cases, however, sprinklings of granules were noted in the interstitial tissue and peripancreatic fat.

Heart. Not uncommonly, the myocardial capillaries were loaded with the dextran granules. In only two cases, however, was there definite evidence of their presence in the stroma, and this was only patchy and light in density. The myocardial fibers, being loaded with glycogen granules, were difficult to assess without very close comparisons with the aqueous control sections. There did not, however, seem to be any localization of dextran within the muscle fibers.

Gastrointestinal Tract. Occasional sections of stomach and intestine were submitted with the autopsy material. No dextran was identified in their walls.

Brain. Tissue blocks from the brains of three patients were studied. Except for the occasional sprinkling of the dextran particles within blood vessels, none was noted.

Soft Tissues. Several of the autopsy cases plus two additional surgically removed specimens included samples of striated muscle, some obtained from wound sites, and also sections of skin. Two

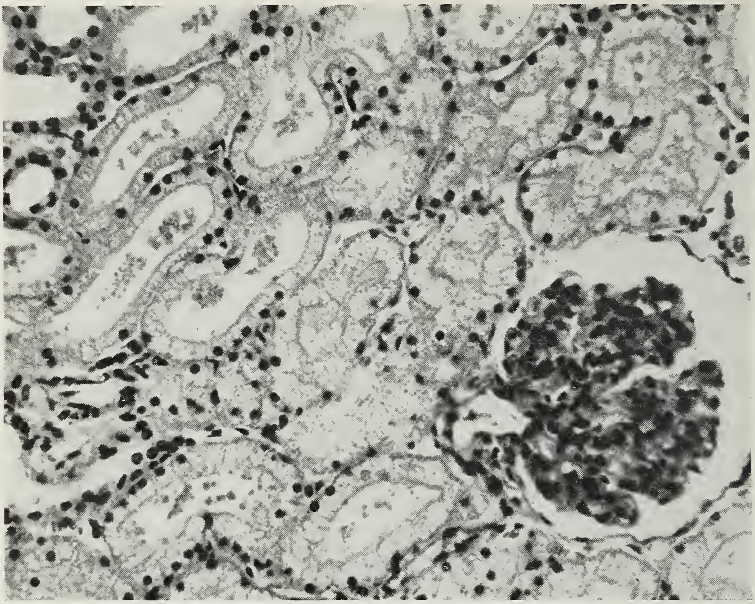

Figure 9 (Case #14, Autopsy #J–3859). "Nephrotic" picture of renal tubular cellular swelling and vacuolization following dextran infusions. The characteristic amorphous intraluminal "casts" are also evident. This soldier suffered very severe wounds, and his postoperative course, despite vigorous therapy, was marked by persistent shock. He received 7,000 ml. of dextran over the 42-hour period of survival following injury.

Hematoxylin and Eosin X 235

muscle sections showed occasional foci of dextran-staining granules within the stroma. The skin sections were all interpreted as being negative save for one notable exception obtained from a severely burned patient, which will be referred to in the Discussion.

Earlier in this report, reference was made to comments by Johnston and co-workers on "overlapping" morphologic features of dextran-induced tubular changes and lower nephron nephrosis. Four of the patients in the present series had a clinical course and histopathologic picture of post-traumatic renal insufficiency (Cases 2, 3, 4 and 12). The kidneys of all four patients presented the typical convoluted tubular changes described above, in addition to the lesion of lower nephron nephrosis. There was no particular difficulty in distinguishing the one lesion from another. Each had histological characteristics distinctive enough to permit a differential diagnosis. The major features of the so-called "dextran-induced" tubular changes seen in both the routine H and E and Mowry PAS preparations were: the sharp confinement of the lesion to the convoluted tubules (and principally the proximal portions); a swollen appearance of the

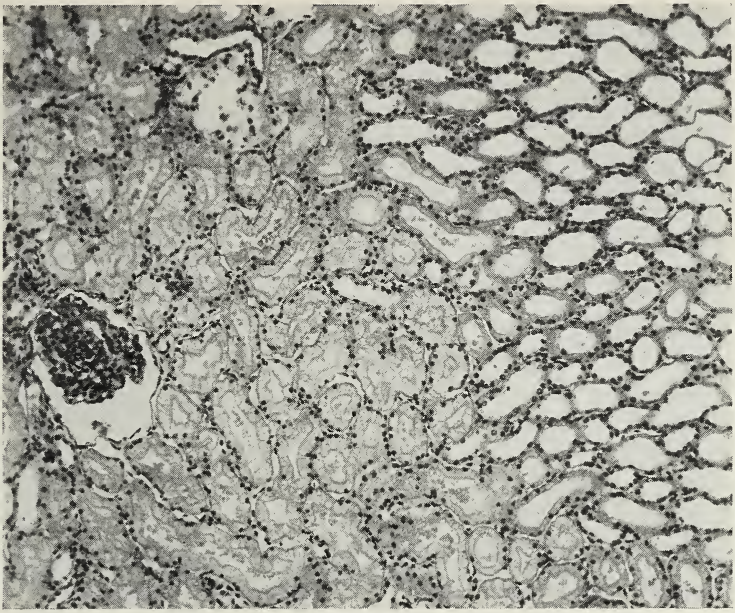

Figure 10 (Case #14, Autopsy #J–3859). A low-power view of the section illustrated in Figure 9. Note the rather sharp confinement of the clear vascular swelling to the cells of the convoluted tubules.

Hematoxylin and Eosin X 100

tubular epithelium often with blurring of the precise cell borders; a tendency of the cell cytoplasm to be clear and finely granular; and the amorphous, eosinophilic, intraluminal material. The histological features of lower nephron nephrosis are well known and differ from these in: (a) the location of the principal alterations (mainly distal nephron instead of proximal convoluted tubules); (b) the presence of distinctive heme-type casts which generally are pigmented and coarsely granular tending to fill the lumina (in contrast to irregularly outlined islands of finely granular to wispy, strandlike masses); (c) the frequent association of tubular epithelial degenerative changes (as compared to none); and (d) the absence of impressive vacuolization and swelling of tubular cells (in contrast to their being the most conspicuous features in the other entity). Interestingly enough, in the patients with associated lower nephron nephrosis, granules of dextran material were occasionally seen dispersed in the heme-cast material (Fig. 11).

Miscellaneous Organs and Tissues. Dextran-stained material was sporadically seen in the interstitial tissue of such organs as bladder, thyroid, adrenal and testis (Fig. 15). As with the occasional focal

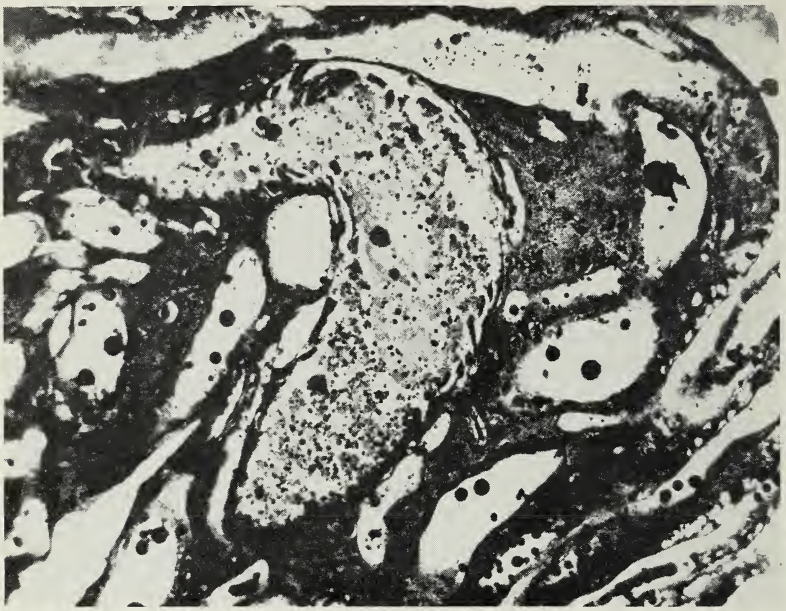

FIGURE 11 (Case #4, Autopsy #J–3315). Dextran aggregates and granules in renal tubules of a patient with post-traumatic renal insufficiency who was given 1,000 ml. of dextran 4 hours prior to death. Note the hook-shaped tubule in the center which contains a typical heme cast (the lightly staining amorphous material) in which are interspersed many irregularly-sized dextran granules.
Periodic Acid Schiff (Mowry) X 240

deposits seen in striated muscle stroma, there was no predictable consistency of these findings.

Discussion

An interpretation of histological observations in this series of 15 autopsies is limited in scope because of the relatively few cases, and because the time intervals involved, from dextran infusions until death, were short, often being only a matter of a few hours. Consequently, one of the major considerations in the evaluation of the effects of dextran on tissues, namely, the question of its possible storage in various cells or organs, can be surveyed only on the basis of such changes being evident very early.

This group of battle casualties presented some unusual considerations with reference to the normal renal clearance of dextran, for most of the patients had suffered periods of profound shock associated with their extensive injuries. The Surgical Research Team demonstrated, by dextran assays in the plasma and urine, the ability of non-oliguric, severely wounded patients to begin renal clearance of dextran within an hour after the start of the infusion. Likewise, the histological

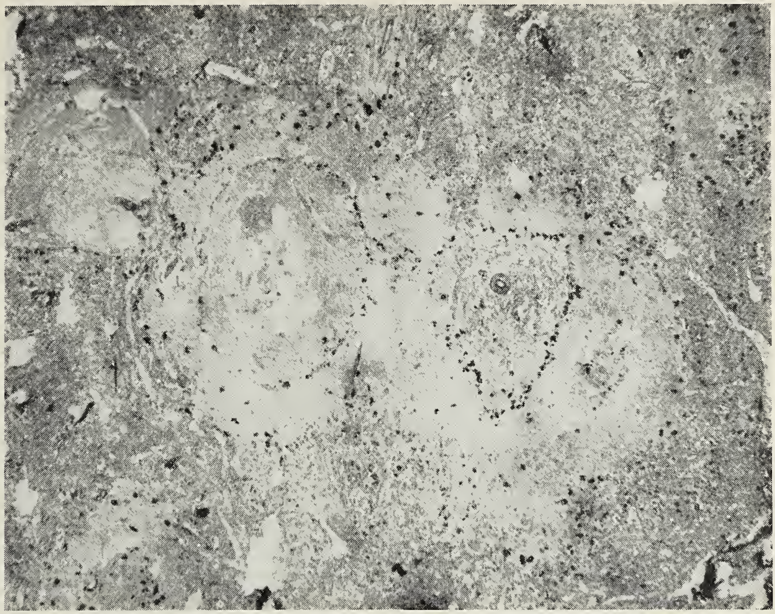

Figure 12 (Rat #M–6633). Survey view of the spleen of a rat which had received bi-weekly dextran infusions (1 ml.) over a 2-month period and then was sacrificed a month following the last injection. Phagocytosed particles of dextran are seen within the reticuloendothelial cells about the periphery of the pale staining Malpighian corpuscles and have a circumferential distribution.

Periodic Acid Schiff (Mowry) X 48

studies revealed the presence of dextran-straining material within the kidneys in patients with the shortest survival times. In only two cases was no dextran identified in renal tissue. In one of these (Case 9), the soldier received a severe gunshot wound of the head and a unit of dextran was started within minutes at the battalion aid station. The patient died, however, within 20 minutes and it is doubtful if he received much of the infusion. The other case (Case 13) should have exhibited dextran in the kidneys; the failure of its demonstration was unexplainable except possibly on the basis of a technical error in tissue preparation.

There were four cases (Cases 2, 3, 4 and 12) that presented a particularly interesting renal study for they showed the pathologic findings of lower nephron nephrosis. One of these (Case 12), in fact, was submitted from the Renal Insufficiency Center where the patient had been under treatment for post-traumatic renal insufficiency. Although there are not available previous data on the actual demonstration of dextran in the human kidney, with particular reference to how long it may remain visualized after intravenous administration,

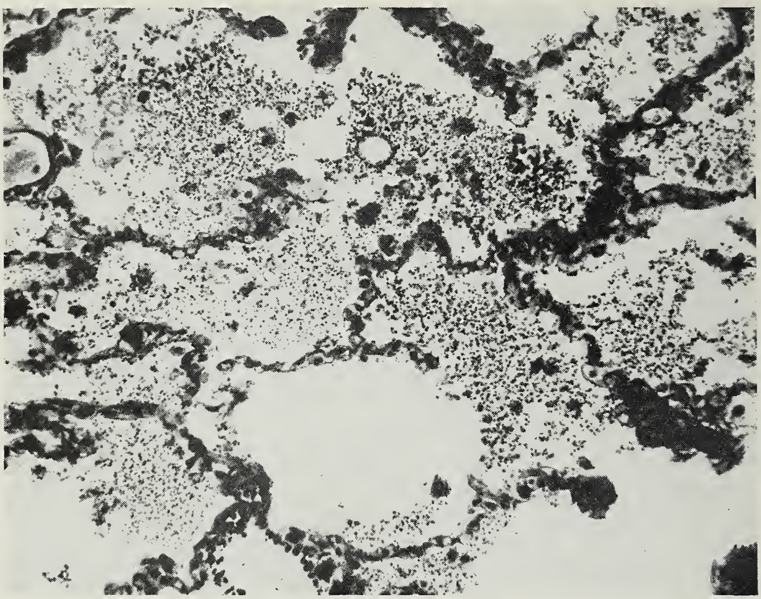

Figure 13 (Case #8, Autopsy #J–3548). Dextran granules within pulmonary alveolar spaces. This soldier received a severe penetrating head wound, associated with profound shock. He was given, in addition to blood, 1,500 ml. of dextran during the 1¼ hours' hospitalization before death. The presence of extravascular dextran particles in the alveoli may have resulted from the shock state. It was interesting to note that the kidney sections of this patient showed no dextran in the tubules, which fact also might be related to hypotension.

Periodic Acid Schiff (Mowry) X 190

two of these cases (Cases 2 and 12) with renal insufficiency suggested a lower excretory rate. They represented the longest intervals between dextran infusions and death in the entire series, 65 hours and 93½ hours respectively. Past studies on the normal renal clearance of dextran and those of the Surgical Research Team on the severely wounded without oliguria indicated that after such intervals the great majority of the substance should have been excreted. The fact that it was still evident in the kidneys of these two patients may have been an abnormal manifestation related to the lower nephron nephrosis. Actual granules of dextran were seen intermixed with the tubular hemoglobin casts in these patients (Fig. 11).

An interesting corollary to these observations in renal failure cases was the data of Howard *et al.* on dextran assays in plasma and urine of the post-traumatic anuric soldier. These revealed a gradual disappearance of the substance in the plasma similar to that of a non-oliguric wounded man, despite renal failure.[18] Rat studies of Bloom,

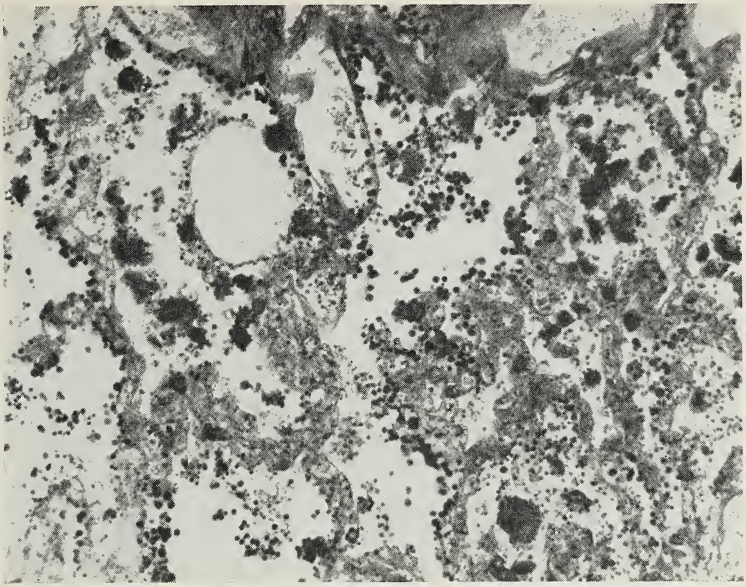

FIGURE 14 (Case #3, Autopsy #J–3200). Dextran particles intermixed with edema fluid in lung tissue of a casualty who suffered from shock throughout a 70-hour post-wound survival period. This observation is of particular interest because of the long time that lapsed (65 hours) after the last dextran infusion. The possibility is raised that this is a manifestation of extravascular immobilization of dextran in a patient with a protracted hypotensive course.

Periodic Acid Schiff (Mowry) X 240

quoted by Johnston and Lundy,[10] showed a 68 per cent disappearance of dextran from the plasma in 24 hours in nephrectomized animals. Such observations as these strongly support the concept of dextran metabolism, and also indicate that the kidneys probably do not play an integral role in the metabolic process. The visualization of dextran particles in renal tubular cells, particularly in the proximal convoluted portions, most likely represents an absorption mechanism of dextran; and this process might be linked to its partial hydrolysis facilitating further metabolism elsewhere in the body.

Concerning the extravascular diffusion of dextran, comment has already been made on its visualization within the interstitial spaces of some organs, where it appeared free and not within phagocytes. Two cases deserve special attention in this regard. Case 8 was that of a Korean who received multiple penetrating wounds of the skull and hands and was admitted to the forward hospital in extremis. In addition to blood transfusions, he was given 1,500 ml. of dextran in the 1 hour and 15 minutes prior to death. Although only a minimal amount of dextran was found in the kidney tissue (within blood ves-

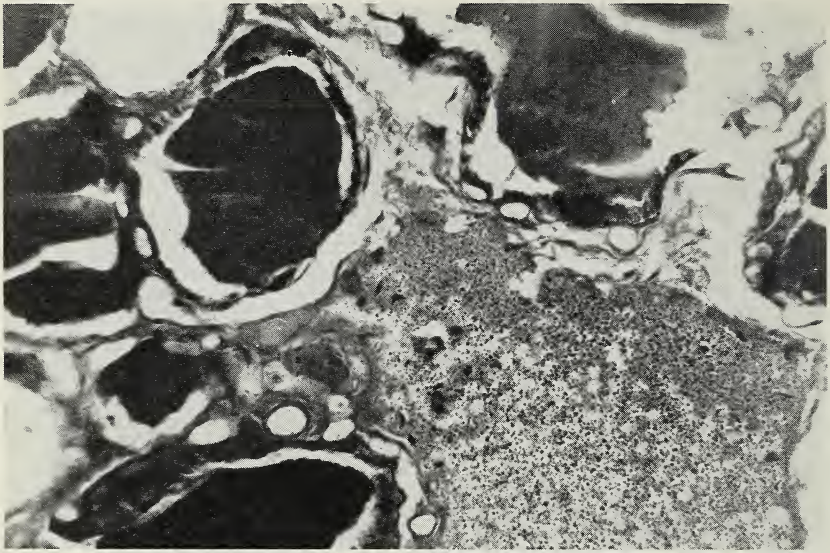

Figure 15 (Case #2, Autopsy #J–3199). A pool of dextran granules in the interstitial connective tissue of the thyroid. (There was no local neck trauma). This soldier suffered from marked postoperative shock, which probably was instrumental in causing this unusually prominent extravascular diffusion. A total of 2,000 ml. of dextran was administered during the 10½ hours before death.
Periodic Acid Schiff (Mowry) X 240

sels), there were areas of marked deposition of dextran-staining granules within pulmonary alveoli (Fig. 13). The dynamics of the transference of the substance from the vascular compartment to the intra-alveolar spaces can only be speculated upon. Similarly, whether the identified granules represent unaltered (unhydrolyzed dextran) is likewise unknown. Bollman[26] performed experiments on the extravascular diffusion of dextran from blood in rabbits and determined that the amount of extravascular dextran was small and that, following hemorrhage, it had little influence on the mobilization of fluid available to the blood.

Another patient (Case 3) was of interest with regard to the possibility of the temporary immobilization of dextran in pulmonary edema fluid. This soldier suffered multiple penetrating wounds of the buttocks and extremities. Despite massive blood transfusions (15,500 ml. in 6 hours), the patient showed a picture of shock all through his 66-hour hospital course. He had also received 1,500 ml. of dextran in the early hours of post-wound treatment. Although there was an interval of about 64 hours from the dextran infusion until death, large amounts of dextran were seen in the lung air spaces associated with a marked degree of pulmonary edema fluid (Fig. 14).

One of the patients (Case 5) received severe burns. Second and third degree burns of 75 per cent of the body surface resulted from the explosion of an oil stove. This patient received 4,500 ml. of dextran during his 47-hour hospital course, which was administered continuously until 5 hours before death. The striking histological finding was a heavy concentration of dextran-staining granules in the skin. Throughout the sections of burned skin, these granules were distributed most prominently in the pools of extravasated fluid in the interstitial spaces of the damaged skin and extended fairly deep into the corium (Fig. 16). As previously noted, sections of skin of other patients failed to show any dextran material. This burn case is of interest because of the virtual absence of dextran identified in any of the organs except the skin. The kidney revealed only minimal amounts, patchy in distribution. Renal function remained good during the patient's course, in spite of which, the dextran contained in the burned skin was not mobilized.

As previously noted, the few specimens of striated muscle and skin obtained from the autopsy cases showed no evidence of dextran localization in the skin and only occasional foci within the interstitial tissue

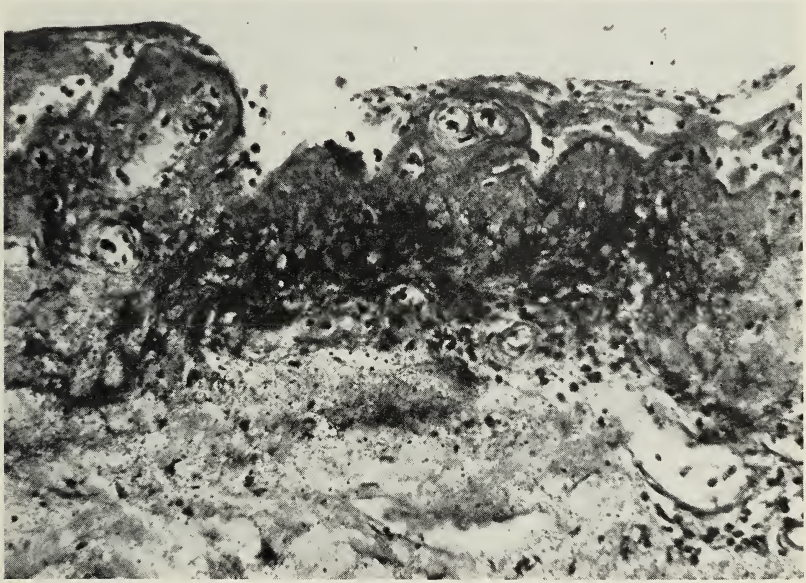

FIGURE 16 (Case #5, Autopsy #J–3426). This is a section of severely burned skin. In addition to blood, 4,500 ml. of dextran was given over most of the 2-day survival period. Note the dispersion of fine granules in the edematous upper corium. The other organs were either negative for dextran or showed only small foci.

Periodic Acid Schiff (Mowry) X 230

of the muscle. In addition, surgical biopsies of both muscle and skin from amputation stumps were studied in two patients who had received dextran several hours previously in the course of treatment. None of these tissues showed evidence of dextran localization. They represented, however, soft tissue from the sites of surgical amputation and not from the actual areas of battle trauma.

Comments have already been made on the nephrotic-like tubular changes observed in kidneys following the administration of dextran. These were consistently present in all cases and, in some, appeared quite striking. These swollen, convoluted tubular cells in ordinary H and E sections presented such a distinctive picture that their recognition in the routine review of autopsy tissues was enough to warrant a strong suspicion that dextran had been administered. On consulting clinical records, this proved to be true in several cases. However, these tubular changes were unassociated with any cellular response or recognizable signs of local tissue reaction. As previous investigators have remarked, they appeared transient and reversible. The Mowry PAS-stained kidney sections correlated nicely with these observations; for in cases showing the most marked tubular epithelial swelling, dense concentrations of dextran-staining material were seen both intracellularly and intraluminally. Arthur Allen, in his textbook on the kidney,[27] refers to the morphologic tubular sequences incident to infusions of hypertonic sugar solutions as giving the pathologic picture of "osmotic nephrosis," a transient effect. The dextran-induced changes seem quite identical to these.

Concerning the reticuloendothelial system as a storage site for dextran, the observations in this series of autopsies indicated no significant phagocytosis in either the spleen or liver. This may have been related to the short time intervals involved, and further studies on patients with longer survival times from infusion to death are needed to help answer the questions of dextran tissue storage. It might be emphasized that although experiments with mice [20] and rats [14] have shown definite evidence of phagocytosed dextran-staining material as long as 3 months following injection, the relative dextran dosage was high and the injections multiple. For instance, a 1 ml. dose of dextran to a 20 gm. mouse is roughly equivalent to an infusion of about 3,000 ml. to an average man. There seems little reason to suppose that the element of tissue storage of dextran in man will prove to be a significant factor. Even in animal studies with multiple large infusions and signs of phagocytosis in the reticuloendothelial body cells, no remarkable tissue changes or reactions have been recognized.[14, 20]

Summary

1. A study of the histological localization of dextran in autopsy tissues of 15 battle casualties in Korea was made.

2. A modified periodic acid Schiff staining method (Mowry) was used. Dextran was distinguished from glycogen by its solubility in water.

3. Dextran rapidly appears in the human kidney tissue and can be visualized in all portions of the nephron. Intracellular granules identified as dextran have been observed in the proximal convoluted tubules of humans and experimental rats, which suggests that dextran absorption and/or metabolism occurs in the kidney.

4. Granules of dextran were occasionally noted in the reticuloendothelial cells of human liver and spleen but these were too minute and scattered for interpretive significance. However, in the rat tissues (after multiple large infusions over a long time) definite and distinct focal phagocytosis was evident.

5. The appearance of dextran within hepatic cells apparently occurs shortly after infusion and is probably associated with a metabolic breakdown of the dextran molecules in this organ.

6. There was scant evidence in this survey of the diffusibility of dextran into tissue spaces except in association with abnormal physiologic states. Specific instances of the latter were cited and included dextran immobilized in the pulmonary edema fluid of those in shock and in the skin tissues of the severely burned.

7. A swelling of renal convoluted tubular cells was noted to be a consistent sequela of dextran therapy. This was correlated with intracellular dextran in the histochemical preparations. These changes were morphologically similar to those following hypertonic sugar infusion and appeared to be nontoxic and transient.

8. Four of the fifteen patients had symptoms of anuria and presented the pathologic findings of lower nephron nephrosis. These were discussed from the standpoints of the effects of anuria on dextran excretion and the significance of dextran in the parenchyma of the anuric kidney for extended periods following infusion.

9. None of the tissues studied (human or rat) showed any recognizable lesions or changes referable to dextran toxicity.

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Chapter 16

Plastic Bags for Intravenous Infusions: Observations in Korea with Saline, Dextran and Blood

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An extensive trial of saline, dextran and blood in plastic bags was carried out during the last 18 months of the Korean conflict. Observations were made on the adaptability of the bag to conditions of shipping, storage and field use. A pliable plastic bag has a number of advantages over a glass bottle as a container for fluids. These advantages are of particular value when considering use in a combat theater. The packed weight of 500 cc. of dextran in a plastic container is slightly less than 1.5 pounds, whereas the weight in a bottle is 2.5 pounds. Tables 1 and 2 outline certain comparative figures concerning transportation requirements of solutions in glass and in plastic containers.[2] The plastic bag withstands shipping well. Of approximately 1,450 plastic bags shipped to Korea, only one was broken. It is believed that plastic containers would be sturdy enough to permit delivery of solutions by parachute drop.

Table 1. Comparative Space Requirements for Glass and Plastic Solution Containers (1,000 cc. capacity) [2]

	Overseas Pack*	
	Glass	Plastic†
Number of containers per pack	12	20
Gross weight per pack (pounds)	64	64
Gross weight per container (pounds)	5. 3	3. 2
Gross cube per pack (cubic feet)	2. 2	1. 5
Gross cube per container (cubic feet)	0. 18	0. 08

* Six glass containers or ten plastic containers in a corrugated box; two corrugated boxes packed in another corrugated box, and an additional outer wooden box lined with waterproof barrier.

† Each plastic container in a square-bottom barrier.

Table 2. Shipping Comparison of Glass and Plastic Solution Containers[2]
(1,000 cc. capacity)

	Glass Container	Plastic Container
Number of liters needed *at destination*	100, 000	100, 000
Over-all breakage rate (estimated)	15%	0
Number needed at point of origin	118, 000	100, 000
Number of cases*	9, 850	5, 000
Gross weight (pounds)	625, 000	320, 000
Gross cube (cubic feet)	21, 600	7, 500
Square feet of space needed to store, stacked 10 feet high	2, 160	750
Number of 20-ton trucks needed to haul	16	8
Men required to load shipment with lift trucks in 8 hours	16	8

*12 glass containers per 64-pound case, 20 plastic containers per 64-pound case.

During the winter months, one of the major problems in the forward aid stations was the freezing of solutions as a result of low temperature. Many glass containers cracked and their contents were lost because of breakage from freezing. The plastic bag was tested under these conditions and, although it was cold enough to freeze the solution within the bag, the bag itself did not break. By squeezing the plastic bag, the speed of administration of a solution can be increased. Empty plastic bags can be disposed of more easily than glass containers. The dangers of broken glass are avoided. No reactions of any type were observed while using the bags.

Normal saline solution in plastic bags (Fenwal-PRJ-681) was used at various echelons of medical care. In testing 350 of these units, each containing 500 cc. of saline, it was found that the solution in this type of bag was very satisfactory. However, since saline is normally used in 1-liter quantities, it would be better to have bags containing 1,000 cc. solution rather than 500 cc. The bag tested was encased for shipment and storage in a small, round, light-weight, metal container for protection. When most of these containers were opened, there were several cubic centimeters of fluid around the bag. This type of metal container was not very satisfactory because it required considerable time to open and it took up more space than the laminated aluminum and paper cover subsequently employed.

Recommendations for Electrolyte Solutions in Plastic Bags

For use in overseas theaters, normal saline solutions, glucose solutions, and lactated Ringer's solution should be put in plastic bags (1,000 cc. per bag), encased in a laminated aluminum and paper cover.

Plastic Bags for Dextran

Two hundred and fifty plastic bags filled with dextran were received in Korea for evaluation. They were used in three battalion aid stations and two forward surgical hospitals. The bags were prepared by Don Baxter Inc., Glendale, California, Model P–1, Lot S–322X, containing dextran injection, 6 per cent, 500 cc. (Fig. 1).

Observations at the Battalion Aid Station.[1, 5, 6] All medical officers felt that it was quite desirable to use plastic bags in the forward area. The size and configuration of the plastic bag was such that it could be carried easily in a jacket pocket, or it could be attached to the aid man's belt by the loop on the bag. An airway was unnecessary,

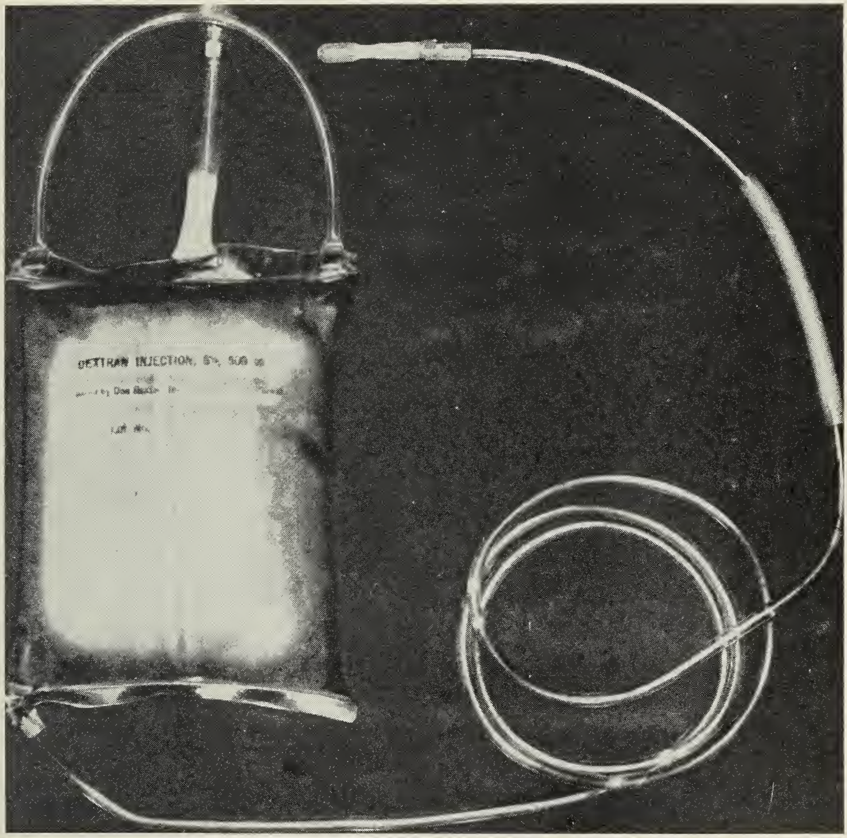

FIGURE 1. Plastic bag filled with dextran (Model P–1, Don Baxter, Inc., Glendale, California). The recipient set is attached and needle is encased in sterile plastic tube at top of bag. A segment of rubber tubing covers an area of the recipient plastic tubing so that injections of other medications can be made into the tubing without subsequent leakage.

thereby eliminating the necessity of extra needles. The contents could be administered very quickly. Flow could be increased either by elevation of the bag or by application of manual pressure. Table 3 shows the different pressures exerted on the plastic bag when it was placed under different areas of three patients on litters. It appeared that fluids were infused more rapidly when the bag was placed under the sacrum. The 17-gauge needle proved difficult to insert, particularly when the veins were collapsed in patients with severe hypotension. It was the general opinion that an 18-gauge needle would be preferable. A drip chamber, although not essential, would be a desirable feature. There appeared to be a weak connection in the unit where the tubing was attached to the bag.

Table 3. Pressures Exerted on Plastic Bag at Different Locations Beneath the Supine Body (Fluid Pressure in Feet)

Weight of Patient	Type of Solution	Location				
		Head	Shoulder	Center of Back T–6	Buttocks	Sacrum
140 lbs.	Saline	1.5	3	3	3	5
	Plasma	1.25	1.25	3	1.5	3
	Blood		1.75	2.5	1.5	2.5
165 lbs.	Saline	1.5	2.75	4.25	2.75	6.75
	Plasma	1.75	2.25	2.5	2.25	3.35
	Blood	1.5	2	2.25	1.75	3
200 lbs.	Saline	1.5	4.25	5.75	4.5	6.25
	Plasma	1.75	2.5	3	3	3.50
	Blood	1.5	1.5	3	2	3

The plastic bag was of considerable value to the surgeon in the forward areas because an aid man could easily carry several in the pockets of his fatigues or looped over his belt. Early replacement of blood volume could therefore be facilitated.

Observations at the Forward Hospital.[3] It was believed that the recipient set needs a drip chamber to permit observation of the flow of solution. Compressing the bag with a blood pressure cuff or squeezing it by hand, although safer than pumping air into the bottle, was not as easy a method of forcing flow. A detachable or universal recipient set might prove advantageous for hospital use because various type of fluids and blood could be administered merely by changing the recipient set without disturbing the needle. The unit appeared to be sturdy in all respects except at the attachment of the recipient tubing to the bag. Two units broke at this junction. The outer container of paper and laminated aluminum foil was quite satisfactory. The units were easily handled and well protected by this container. No reactions were seen from dextran in plastic bags.

Recommendations for Dextran in Plastic Bags

It is recommended that dextran in plastic bags be standardized. A plastic bag, similar to the item tested and packed in laminated aluminum foil, would be acceptable for use in the division area if the following revisions are made: (1) an 18-gauge needle to be substituted for the present 17-gauge needle; and (2) the point of attachment of the tubing to the bag to be made stronger and more durable. For use in the hospital, it is desirable to have detachable tubing and a drip chamber. The plastic containers for hospital use should be a standard bag with interchangeable recipient sets for all electrolyte solutions and dextran.

Plastic Bags for Blood

A total of 250 units of blood in plastic bags was received in Korea and approximately 200 units were used in the treatment of patients. The bags were Fenwal plastic blood packs, catalogue No. JA–2 (C), with 75 cc. of acid-citrate-dextrose solution. No bags were broken and transportation was facilitated because of the decreased weight. The blood pack was easily used when blood was given by the normal rate of drip. The small slit at the top of the bag was not suitable for hanging the bag during administration. The recipient set attached easily to the bag. The drip chamber filled too easily and obscured vision of rate of flow. The plastic tubing (with insert of rubber tubing) proved to be very satisfactory for injection of other medications.

The bag was unsuitable, however, for use in a forward hospital because it was impossible to give blood rapidly under pressure to several patients at the same time. No practical method was found for forcing blood out of the plastic bag. It was possible to squeeze the bag, but it was impractical to assign one corpsman to each bag when 8 or 10 pressure transfusions were being given simultaneously to various patients. The use of the Fenwal plastic box, with rubber bag insert for exerting pressure on the blood pack was impractical. The chief deterrent to the acceptance of the present plastic container for blood is that the bag is not easily adapted to the rapid administration of blood. This is extremely important because about 30 per cent of the blood given in a forward surgical hospital must be given under pressure.

Storage of Blood in Plastic Bags. Serum potassium determinations were carried out by Lieutenant John B. Frawley on several units of blood in bottles and blood in plastic bags. The bottles and bags were filled in the United States and were then shipped to a forward hospital under identical conditions. The results of these determinations are outlined in Table 4. In the 19-day-old blood, the average serum potassium of blood in plastic bags was 28 mEq. per liter in comparison to 18 mEq. per liter for blood in bottles. The 20-day-old blood showed about the same difference in potassium concentration. These results are supplementary to earlier studies by this laboratory which indicated that blood in Fenwal and Cutter plastic bags compared favorably with blood in bottles during shipment and storage.[4]

Desirability of Plastic Bags for Blood. It would be desirable to have some type of plastic container for blood and all intravenous solutions. It would be particularly advantageous to have a plastic bag from which blood could be given under pressure. The present practice of pumping air into a bottle to force rapid infusion of blood carries the danger of air embolism. At least four casualties died from air embolism during the last year of the Korean conflict. If practical, it might be possible to put a second plastic bag outside the bag containing blood into which air could be pumped to exert pressure on the inner bag. This would permit a rapid and safe method of administering blood under pressure.

Recommendations Concerning the Plastic Bag for Blood

A plastic container for blood is desirable.

The plastic blood bag was unsuitable for field use because blood in these bags could not be satisfactorily given under pressure. Continued efforts should be made to develop a bag or suitable attachment whereby blood from the plastic container could be forced into a vein under pressure.

Summary

In the latter part of the Korean conflict, observations were made on the use of plastic containers, 350 filled with saline, 250 with blood, and 250 with dextran. When covered with paper and laminated aluminum foil, these bags were most satisfactory for electrolyte solutions and dextran. The plastic bag for blood was not suitable because transfusions could not be given satisfactorily under pressure to a large number of patients at the same time.

The following recommendations are made:

Table 4. Plasma Potassium Levels of Stored Blood Bottles and Fenwal Plastic Bggs

Blood in Bottles						Blood in Plastic Bags					
No.	Age Days	mEq./L. K	No.	Age Days	mEq./L. K	No.	Age Days	mEq./L. K	No.	Age Days	mEq./L. K
2	19	18. 3	20	20	21. 3	1	19	27. 6	19	20	27. 9
4	19	16. 8	22	20	21. 6	3	19	30. 0	21	20	31. 5
6	19	15. 9	24	20	18. 9	5	19	26. 1	23	20	29. 4
8	19	19. 8	26	20	21. 0	7	19	30. 3	27	20	30. 6
10	19	25. 2	28	20	23. 4	9	19	29. 7	29	20	26. 7
12	19	16. 2	32	20	19. 2	11	19	28. 5	31	20	31. 5
14	19	18. 6	34	20	21. 0	13	19	28. 8	33	20	29. 7
16	19	18. 0				15	19	30. 0	35	20	31. 5
18	19	17. 4				17	19	24. 9	37	20	29. 7
									39	20	28. 8
									41	20	33. 0
Averages:		18. 4			20. 9			28. 4			30. 0

a. Within the limitations of this study it is recommended that plastic bags, filled with dextran, be standardized for use within the division area. The recipient set should be attached to the bag but a drip chamber would be desirable.

b. Plastic bags (1,000 cc. capacity) should be standardized for overseas use for glucose, saline, glucose and saline, and lactated Ringer's solution. Similarly, plastic bags (500 cc. capacity) with interchangeable recipient sets should be standardized for dextran for hospital use.

c. Further efforts should be carried out to develop a suitable plastic bag for blood. These bags must be able to administer blood under pressure satisfactorily in order to meet the requirements of a forward hospital.

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Chapter 17

Clinical Observations on the Role of Vasoconstrictors In the Treatment of Hypotension Following Injury

(A Study of Battle Casualties)

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A fundamental principle of resuscitation is that the physician should recognize and correct any injury and any deficiencies in the body's response to the injury. The delineation of the indications for the use of vasoconstrictors should therefore be based on the results of a study of the response of the autonomic nervous system to trauma. Such studies are, to date, incomplete. Meanwhile, clinical experiences have delineated the general areas of usefulness of this therapy as observed in the resuscitation of almost 5,000 battle casualties in Korea. These casualties represent young men (18–30 years) who were in good health prior to injury. Admission to the forward surgical hospital, where these observations were made, occurred on an average of 3.5 hours after injury.

The Preoperative Phase

Resuscitation in the preoperative phase consisted primarily of the control of hemorrhage and the correction of the blood volume deficiency. An occasional problem in the preoperative resuscitation of the very severely injured battle casualty was the development of a hypotension which was somewhat refractory to transfusion. As a result, transfusions of the order of 5,000 to 10,000 ml. of blood (10 to 20 units) were occasionally used during this period. Much of the blood was used after the apparent control of hemorrhage. In spite of transfusion of this degree, the blood pressure was occasionally slow to respond. This was an unusual experience at this early period in resuscitation, and experience with the vasoconstrictors was limited. The following patient is typical of the four such patients studied.

Patient No. 1. This Korean soldier, age 25 years, was wounded at 1040 hours, 26 April, 1953. The injury, inflicted by artillery shell fragments, included incomplete amputations of both legs, avulsive wounds of the thighs (25 cm. diameter), fracture of the left humerus, fracture of the bones of the right elbow, and avulsive wounds of both hands.

On arrival at the hospital, his vital signs were unobtainable. After 2,000 ml. of blood intravenously and 2,000 ml. intra-arterially, his blood pressure was 90/70, pulse rate 108 per minute. Tourniquets had been placed around the legs so that external bleeding was not too extensive.

As transfusion was slowed, his pressure dropped to 80/62.

One and one-half hours after admission and after 4,500 ml. of blood, noradrenalin was administered via a drip of blood at the rate of 40 to 56 μg./minute. His pressure rose transiently to 94/70 and then dropped to 70/60 in spite of the continued, slow administration of 1,000 ml. of blood containing 8 mg. of the drug. The drug did not affect the pulse rate which remained at 104 to 108 per minute. Another 1,000 ml. of blood was given rapidly and his pressure again rose to 102/60.

Although his pressure would respond to very rapid transfusion, it could not be stabilized and the vasoconstrictor did not appear to reduce his transfusion requirements. In the hope that débridement might reverse his course, surgery was undertaken. Under minimal anesthesia and employing four surgical teams simultaneously, débridement was undertaken, but he died at the conclusion of the 30-minute procedure.

Experience with the vasoconstrictors during the preanesthetic phase was too limited to permit generalization, but the only preoperative indication for their use which was recognized was in patients with an anatomical wound of the nervous system such as the patient with severe hypotension secondary to an injury of the central nervous system.

The Operative Phase

A fundamental difference between the battle casualty and the nontraumatic civilian patient is that the battle casualty, as he comes to anesthesia, often has a fully developed autonomic response.[1] Anesthesia blocks this response. Pentothal, universally used in the Korean Theater, has been described as an autonomic depressant.[2] The casualty who was well prepared by transfusion for surgery could tolerate such a blockade; the patient who was inadequately prepared could not. In the latter patient, a sharp drop in blood pressure occurred. This was noted time and time again. To the severely injured men, this drop occasionally proved fatal. Particularly in the presence of abdominal injuries where bleeding was often masked, the patient might begin anesthesia with a decreased blood volume. The blood pressure, being maintained at this time by vasoconstriction, dropped sharply with the induction of anesthesia.

The effect of noradrenalin and other vasoconstrictors in preventing or treating the vasodilatation of anesthesia has been so widely experienced by anesthesiologists as to need no documentation here. Its effectiveness was repeatedly demonstrated by anesthesiologists in the Korean Theater. The hazard in its continued use was that it sometimes continued to mask a blood volume deficiency. This danger could only be minimized by the alertness of the surgeon and anesthesiologist.

The principle is that the deficiencies in response must be overcome. Pentothal, and other anesthetic agents to a certain extent, apparently block the response of the sympathetic nervous system. As this system is often in full response at this time, its coincident augmentation with vasoconstrictors would often appear advisable.

The Postoperative Phase

Following large transfusions, postoperative hypotension occurred not infrequently. It developed during the first 6 to 18 hours after operation and persisted for a period up to 48 hours, usually ending in recovery, but sometimes in a fatality. Therapy with additional whole blood characteristically led to the restoration of a normal blood pressure. This discussion, however, is based on the occasional casualty who remained refractory to transfusion.

The mechanism of this hypotension is uncertain. That it stems from an absolute, continuing deficit in circulating blood volume has not been disproved,[3] but sometimes seemed impossible. In an occasional patient it would appear to be the result of a deficiency in the cardiovascular system.[4] Although improbable, it may be that the anesthetic agents are so slowly metabolized or their effects so slowly reversed after severe trauma that the patient's vascular system remains under their influence for many hours.

The vasoconstrictors have been used in two phases of this syndrome. In one, the pressure can be maintained at 80 to 90 mm. systolic by continued transfusion; in the other, the pressure continues to drop in spite of transfusion.

Moderate, Sustained Hypotension

Patient No. 2 This soldier, age 22 years, weight 190 pounds, was wounded by shell fragments at 0200 hours, 7 February 1953. The wounds included multiple perforations of the small bowel and sigmoid; two holes in the urinary bladder; severe, comminuted, compound fractures of the left femur and left tibia; and multiple soft tissue wounds of the buttocks and abdominal wall.

At the collecting station, 0345 hours, he was given 1,000 ml. of blood. At the clearing station his blood pressure was 120/70; he was given another 1,000 ml. of blood. He arrived at the forward surgical hospital at 0645 hours. His pressure was normal but he appeared critically injured.

Prior to operation he received an additional 2,000 ml. of blood. His hematocrit at this time was 49 per cent, and his white blood cell count was 4,700.

Operation, lasting 7 hours, was begun at 0800 hours. It consisted of repair of eight holes in the bowel, three bowel resections, colostomy, cystostomy, and débridement of many wounds. His pressure was maintained with difficulty. His operative blood loss, measured by the washed sponge technic, was 1,670 ml. He was given 3,500 ml. of blood during this time. With the onset of pentothal induction (later nitrous oxide, oxygen, ether), his blood pressure fell from 106/84 to 60/40; his pulse rising from 100 to 116. An intravenous drip of 500 ml. of blood containing 4 mg. of noradrenalin resulted in an immediate rise in his pressure to 90/50 and then 100/60. Later in the operation this drug was much less effective.

Peritoneal contamination was massive. A hemoclastic reaction was strongly suggested by the postoperative drop in his white blood cell count to 1,850. His platelet count at this time was 710,000; clot formation was normal.

His hematocrit postoperatively was 55 per cent. His blood pressure ranged 90 to 100 systolic, 50 to 60 diastolic, and his pulse rate ranged around 120 per minute.

One hour after operation his blood volume (T–1824) was 4,720 ml., plasma volume 2,220 ml. One thousand ml. of dextran was then given over a period of 4 hours. No changes in vital signs occurred. His hematocrit was then 42.5 per cent, his plasma volume was 3,070 ml., blood volume 5,200 ml. (Evans Blue).

Throughout the first postoperative night his pressure ranged about 80/50, pulse rate 130, respirations 40. His subcutaneous veins were not prominent. On the first postoperative morning his pressure was 86/56. Blood, 1,500 ml., and dextran, 1,500 ml., were then given over a period of 7 hours. His blood pressure rose to 112/80, pulse rate 104. His plasma volume then measured 3,750 ml.; blood volume 5,980 ml.; hematocrit 41 per cent. He was then given another 500 ml. of blood.

During the second postoperative night his pressure again fell to 94/64, pulse rate 140. No bleeding was evident. Dextran, 500 ml., was given at 0330 hours (9 February 1953) with no obvious improvement. He had at this time received 9,000 ml. of blood and 2,000 ml. of dextran.

Noradrenalin, 4 mg./1,000 ml. of 5 per cent glucose in water, was dripped in at a rate of 1.6 μg/minute. The blood pressure gradually rose to 120/70, pulse 140 (Fig. 1). He became very flushed and his capillary refilling was rapid. Oxygen, per nasal catheter, changed his appearance from a cyanotic to a reddish flush.

Throughout the second postoperative day, his blood pressure was maintained at 115–125/65–80. His pulse rate gradually fell to 115 per minute. The noradrenalin meanwhile was slowed to 0.6 μg./minute and on the third postoperative day was withdrawn. His pressure was maintained thereafter. A total of only 1.6 mg. of the active base was used during the postoperative period.

At 2115 hours, 10 February, his blood volume measurement was repeated. His plasma volume measured 3,600 ml., blood volume 6,100 ml. Throughout this period when his pressure was above 90 to 100 mm. systolic, he diuresed rapidly. His subsequent course was uneventful.

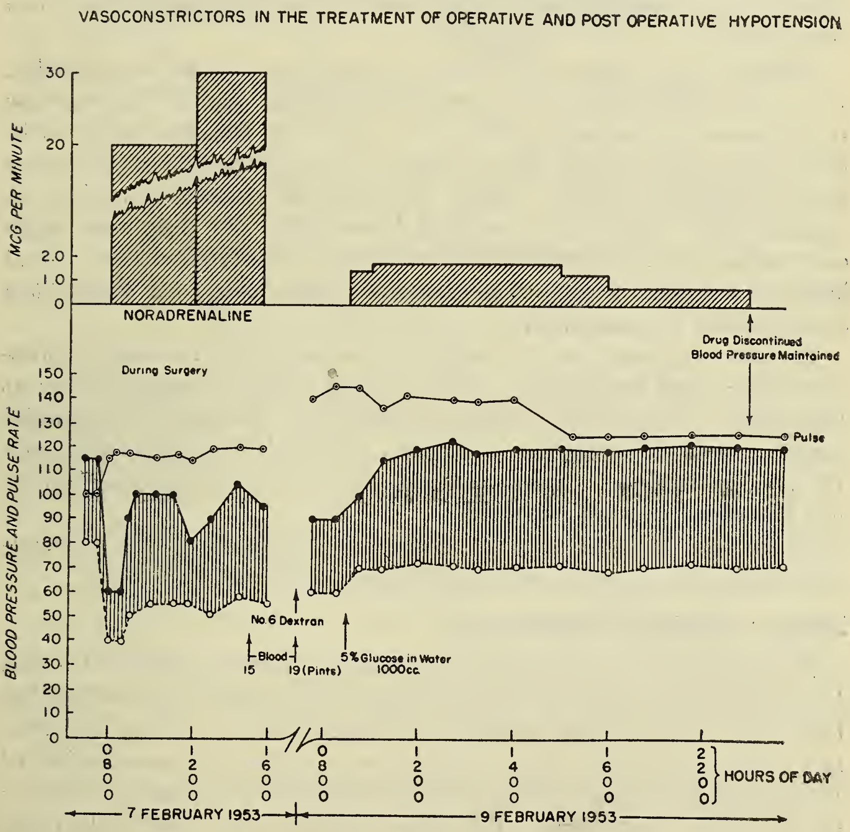


FIGURE 1. After a prolonged postoperative perlod of hypotension (90 mm. systolic), his pressure responded to an extremely small dose of noradrenalin (Patient No. 2).

Patient No. 3 This 26-year-old American soldier was wounded at 0500 hours, 24 February 1953, by mortar shell fragments. The wounds included a scalp laceration, perforation of the liver and kidney, traumatic amputation of the right thigh, and multiple soft tissue injuries.

At 0600 hours, on arrival at the battalion aid station, his blood pressure was unobtainable and he was unconscious. Both pupils were constricted. After 320 ml. of albumin and 1,500 ml. of saline, his pressure was 80/40.

On arrival at the hospital, 0740 hours, by helicopter, his pressure and pulse were again unobtainable. Following 6,000 ml. of blood by 1600 hours, his pressure was 140/80, pulse rate 120. Operation was then begun under pentothal, nitrous oxide, and ether anesthesia. His pressure immediately fell to 90/60, pulse rate 124. The pressure was still low, 80/50, 3 hours later, after a total of 9,500 ml. of blood. Meanwhile, re-amputation, débridement and laparotomy had been completed.

Infusion of the 20th unit of blood, containing 4 mg. of noradrenalin, was started just prior to the completion of operation. The response in pressure was immediate (Fig. 2). The drug was gradually withdrawn and was stopped after 5 hours. Two hours later the pressure again dropped to 90/50. Again the pressure responded rapidly to noradrenalin. Three and one-half hours later the drug was again discontinued and his pressure was subsequently maintained at a normal level. Less than 2 mg. of noradrenalin had been used during the entire period of treatment.

He was evacuated on the second day after injury because of post-traumatic renal insufficiency. He had not regained consciousness at that time. Concussion, without evidence of increased intracranial pressure, was the tentative diagnosis. He died of renal insufficiency 19 days post-injury. There was no evidence of intracranial injury. Fat embolism was not excluded.

These two patients represent the rare exceptions where vasoconstrictors appeared to be beneficial in the postoperative period.

Severe, Sustained Hypotension

Patient No. 4. A 24-year-old American soldier was admitted to the forward hospital at 0530 hours, 9 hours after injury by an exploding land mine. His injuries included compound fractures of the humerus and radius, severance of the radial artery, extradural penetration of the frontal bone, perforation of the small bowel, and massive injuries of the lower extremities. His blood pressure was 50/30, his pulse unobtainable. After 4,000 ml. of blood, his pressure had returned to 110/78 and his pulse rate was 110 per minute. With pentothal

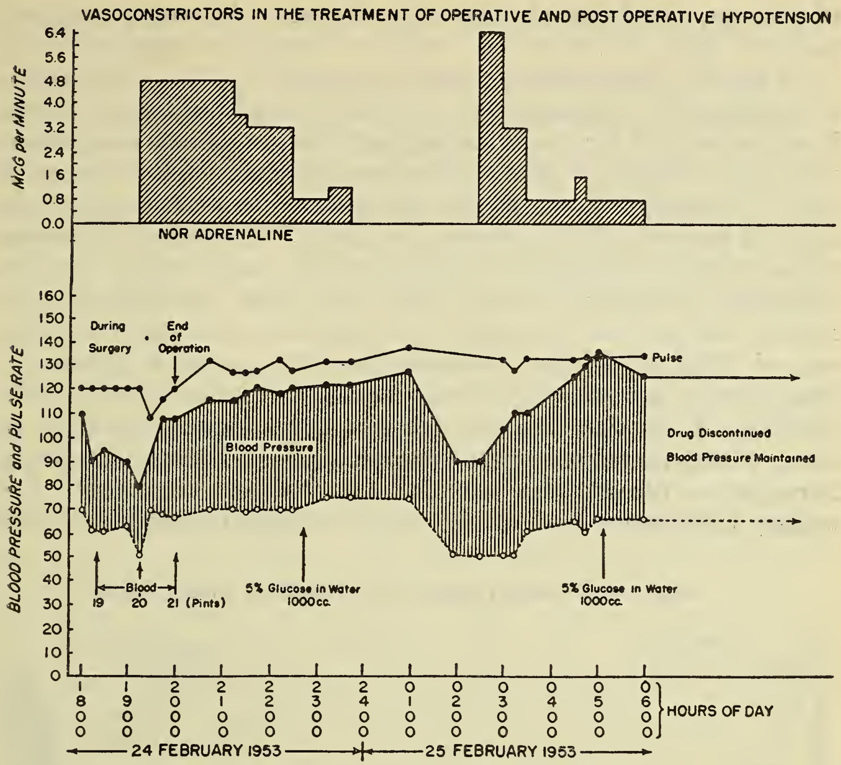


Figure 2. As with the preceding patient, the mild postoperative hypotension responded to noradrenalin (Patient No. 3).

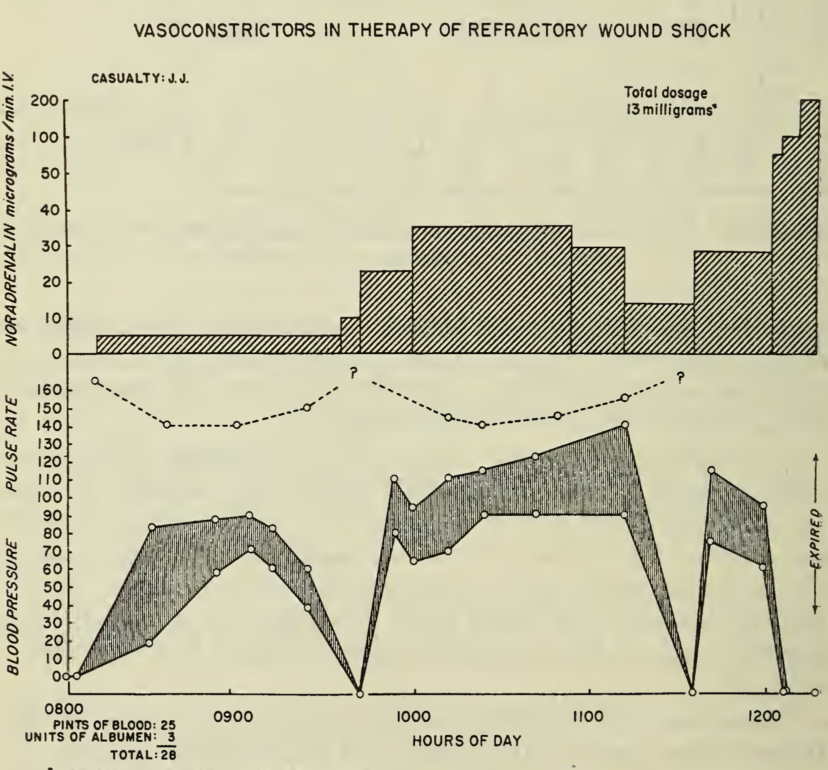
induction, his blood pressure became unobtainable. Five milligrams of neosynephrine by rapid intravenous drip resulted in a transient rise in pressure to 100/50 but again his pressure became unobtainable. Intra-arterial transfusion was then begun.

Operation was continued under ether anesthesia, administered endotracheally. Two and one-half hours were required to repair the small bowel and débride the larger wounds, including the extradural wound. His blood pressure was maintained throughout all but the induction phase by the intra-arterial and intravenous administration of 4,000 ml. of blood (8,000 ml. total since admission). His operative loss of blood (washed sponge technic) was estimated at 3,250 ml.

During the night following operation, his blood pressure was maintained in the range of 110/60, pulse 140 by the administration of an additional 4,500 ml. of blood and 300 ml. of albumin. Twenty-four hours after admission and after a total of 12,500 ml. of blood, 300 ml.

of albumin, and 2,000 ml. of 5 per cent glucose in water, the blood pressure again fell until it could no longer be obtained.

An infusion of noradrenalin was then begun (Fig. 3). (The dosage of noradrenalin is expressed in terms of the active base, 1 mg. of which is equivalent to 2 mg. of the Lephophed bitartrate preparation which was used.) During a steady intravenous infusion of the drug at a rate of 5 μg./minute, the patient responded with an immediate rise in blood pressure which persisted for 1 hour. Thereafter he became refractory to this dosage. The blood pressure could still be titrated by greatly increasing the dose. Three hours after the drug had been started, his pressure was 140/90 and his pulse rate was 156. The rate of infusion was then decreased from 28 μg. to 14 μg./minute. Immediately thereafter his blood pressure and pulse became unobtainable. A transient response followed the subsequent increase in dose. Finally, 4 hours after starting the drug, he became completely refractory to noradrenalin and died a few minutes thereafter. His axillary temperature rose shortly before his death to 106° F. A total



*EXPRESSED IN TERMS OF ACTIVE BASE OF LEVOPHED

FIGURE 3. The development of refractoriness to noradrenalin (Patient No. 4).

of 13 mg. of the active base (26 mg. of the commercial preparation) was used.

Patient No. 5. This 20-year-old American soldier was wounded by mortar shell fragments at 1200 hours on 24 October 1952. He sustained injuries to the left brachial artery, a compound fracture of the left humerus, retroperitoneal perforation of the rectum and bladder, and multiple penetrating wounds of the buttocks, thighs and legs. He was given 1,500 ml. of blood at the battalion aid station and arrived at the hospital 3 hours after injury with a blood pressure which was unobtainable. While receiving blood, he was given pentothal and ether and the brachial artery was ligated.

No operative procedure beyond control of hemorrhage was attempted. After 36 units (additional) of blood, 2 units of albumin (200 ml.) and 2 units of dextran (1,000 ml.), his pressure began to fall from its peak of 80 mm. Hg. systolic. Because blood replacement had provided a blood volume which could not conceivably have been deficient, with little bleeding, and because his arterial pressure was falling and he presented no evidence of increased venous pressure, the use of vasoconstrictors was elected. In view of the experiences with the other drugs, pitressin was selected for trial. Figure 4 demonstrates the moderate but transient response to the drug. It was necessary to increase intravenous dosage of the drug gradually, but, after 11 hours, he became completely refractory even to massive doses. The refractoriness was evidently a peripheral effect for there was still no sign of increased venous pressure as might have been anticipated from the vasoconstrictive effect of pitressin on the coronary vessels. A total of 200 units of pitressin was used.

Finally, after his blood pressure had been unobtainable for 6 hours, he was given a slow intravenous drip containing noradrenalin. His pressure responded immediately, but after an hour he developed a complete refractoriness to this drug also and died a few minutes thereafter.

Patient No. 6. This 21-year-old American soldier was wounded at 2000 hours, 6 November 1952, by mortar shell fragments. His wounds included perforation of the spleen, stomach, small intestine, colon, popliteal artery, and multiple wounds of the extremities. He was admitted to the forward surgical hospital 4 hours later. He was profoundly hypotensive at this time. Following transfusion, operation was performed under pentothal, nitrous oxide, oxygen and ether.

He was moderately hypotensive throughout the 5-hour reparative operation in spite of the administration of 22 units of blood, 10 of them after the apparent control of hemorrhage. After moving the patient to the ward, his blood pressure was 80/40 but it rapidly became unobtainable. Neosynephrine, 10 mg. in 500 ml. of blood,

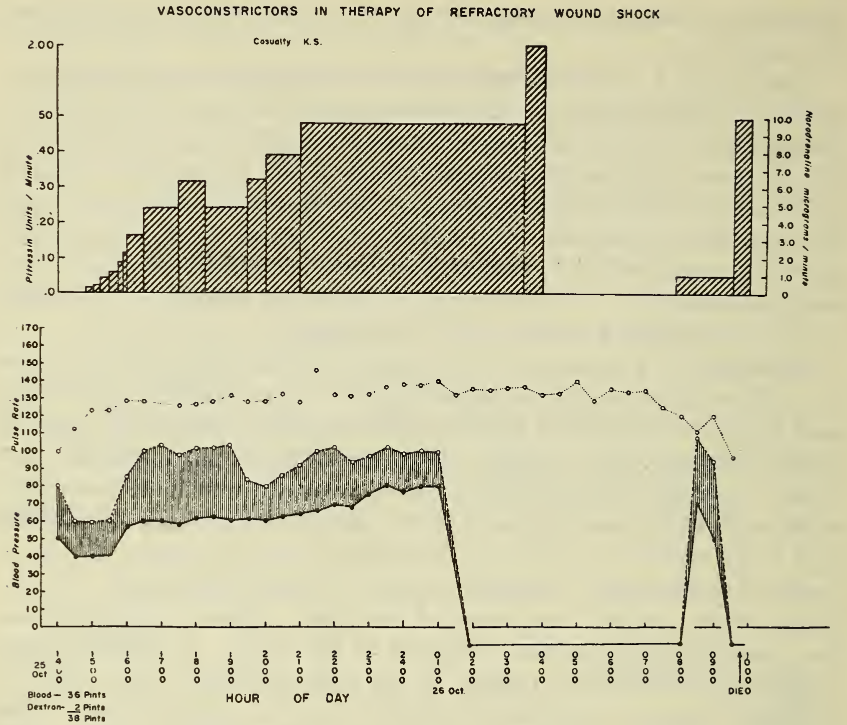


FIGURE 4. Having become refractory to pitressin, the blood pressure responded transiently to noradrenalin (Patient No. 5).

was given by rapid drip. His pressure rose to 70/50 and remained at that level during the administration of the drug.

He subsequently proved refractory to further transfusion and to neosynephrine and died in shock approximately 20 hours later.

Patient No. 7. The casualty, a 22-year-old American soldier, was wounded at 1900 hours, 23 November 1952, by the explosion of a land mine. The injuries sustained included perforation of the left lateral sinus, penetration of the buttocks, arm and both legs, fracture of the femur, and perforation of the sigmoid colon.

At the collecting station he was given 2,000 ml. of blood after which his blood pressure rose from "shock" level to 100/60.

On admission to the forward surgical hospital, 3.5 hours after injury, his blood pressure was 70/40. He remained in the shock ward until a total of 13 units of blood had been administered. His blood pressure ranged between 95/50 and 0 with a pulse rate of approximately 140 to 150. After 24 units of blood, his pressure was 124/70, pulse 120. A sigmoid colostomy was carried out under pentothal, nitrous oxide, and ether. After the repair of the lateral sinus and after the administration of 31 units of blood, his blood volume (radioactive chromium technic) was normal. His pressure, however, fell postoperatively to 44/30. Noradrenalin (32 mg. total) was given intravenously in the next 3 units of blood (17,000 ml. total) over a period of 4 hours. His pressure rose rapidly to 100/40, pulse 124, but he became refractory to the drug and died at the end of the fourth hour.

Patient No. 8. This American soldier, wounded by shell fragments, was admitted to the forward surgical hospital 6.5 hours after injury. His wounds included perforation of the jejunum and transverse colon. He was given 12.5 units of blood and 1 unit of dextran between the time of wounding and the completion of operation. Peritoneal contamination was massive. At the end of operation he experienced a hemoclastic reaction with a fall in blood pressure. Recovery from shock was spontaneous.

Thirty-three hours after injury his pressure fell to 70/40. His blood culture at this time revealed *E. coli,* beta hemolytic Streptococcus, and nonhemolytic Staphylococcus. Noradrenalin was given in massive doses but there was no persistent response in blood pressure, and he died shortly thereafter.

These patients represent the rather fruitless response to vasoconstrictors in severe postoperative shock. The drugs did not appear to meet the basic deficits of this specific group of patients.

The next two patients are described primarily because one demonstrated the development of refractoriness to one vasoconstrictor while responsive to still another, and the second developed refractoriness to neosynephrine. They are not typical of the problems more frequently encountered.

Patient No. 9. This American soldier was wounded by mine fragments at 1400 hours, 20 May 1952. Injuries included a severe injury to the right eye, laceration of the spleen, left kidney, stomach and diaphragm, and fracture of the left humerus.

He was given 100 ml. of albumin at the battalion aid station and reached the hospital approximately 1 hour after injury. His blood pressure was unobtainable. His hematocrit was 38 percent.

After receiving 3,500 ml. of blood, his pressure rose to 120/80. Reparative surgery, including removal of the spleen and eye, was uneventful. He was supported during the operation with an additional 2,000 ml. of blood.

On the third postoperative day he eviscerated through the laparotomy wound. Operative repair, requiring 1 hour, was associated with a blood pressure of 90 to 100 systolic, 50 diastolic. His pressure postoperatively ranged between 80 and 120 systolic, and between 60 and 80 diastolic. His hematocrit was 46 per cent. The total amount of blood administered during his hospital stay was 15 units.

On the sixth day after injury, his pressure, having previously responded to transfusion, fell to 60/40. As blood and fluid had been carried to a degree considered at that time to be optional, vasoconstrictors were used. It should be noted that at this time the patient had been expelling gas per rectum and was not distended. He did not have signs of residual peritonitis.

His response to vasoconstrictors is depicted in Figure 5. Massive doses of neosynephrine and noradrenalin were necessary to maintain his pressure. He developed a refractoriness to one drug while still responsive to the other. When his pressure fell, anuria would occur, but when the pressure was raised by vasoconstrictors, a fairly normal urinary output resulted.

Clinical evidence of a frontal lobe damage was confirmed at autopsy; there was a 2.0 cm. area of necrosis of the frontal lobe adjacent to the injured orbit.

Patient No. 10. This 21-year-old American soldier was accidentally shot with a .45 caliber pistol at 1500 hours on 24 January 1952. The

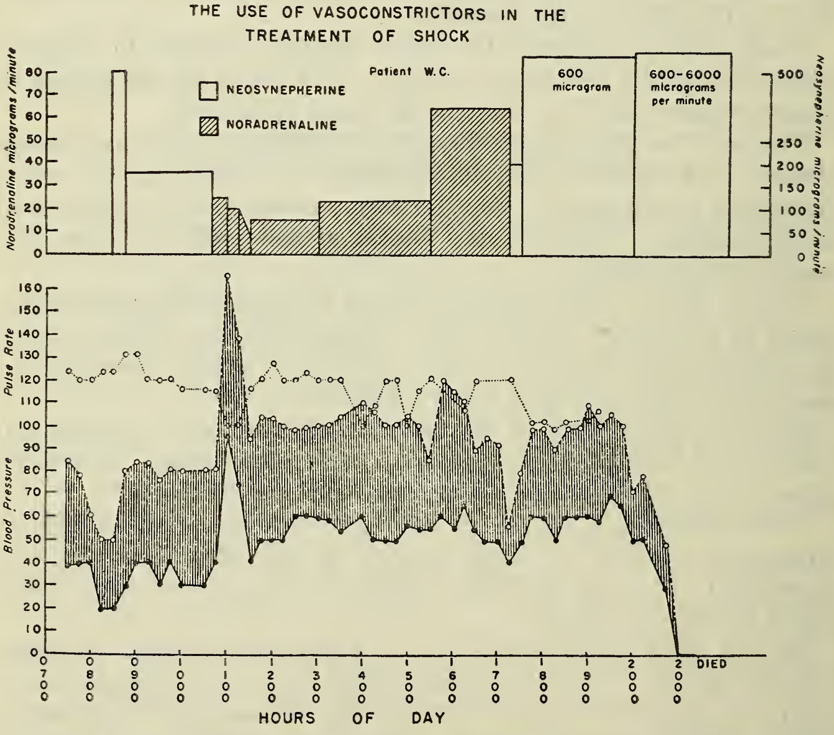


Figure 5. This patient developed a refractoriness first to noradrenalin and then to neosynephrine (Patient No. 9).

missile perforated his stomach and jejunum and lodged lateral to the vertebral column. He was admitted to the hospital at 1700 hours with blood pressure of 120/60. He was given 1,000 ml. of blood, during which time the bowel perforations were closed.

Twenty-four hours after operation, with a course apparently otherwise smooth, oliguria was noted. His blood pressure at this time was unobtainable, although his cerebral blood flow seemed good as the patient was lying flat, reading a newspaper.

Evidence of a paralysis of the lower portions of the spinal cord was discovered. Paralysis had not been present at the time of admission. During the ensuing 12 hours his pressure could be titrated with a slow drip of neosynephrine. He soon became refractory to the drug and died shortly thereafter. There was no indication by blood culture or temperature of a septicemia. He had received a total of only 2,000 ml. of blood.

Autopsy revealed no evidence of vertebral or spinal injury except the presence of bloody spinal fluid, which had been demonstrated by a spinal tap prior to autopsy.

Summary

In observing the results of resuscitation of almost 5,000 battle casualties over a period of 18 months at a forward hospital in Korea, clinical observations have been recorded on the experiences with vasoconstrictors.

Their usefulness prior to operation was not fully evaluated but appeared limited to an occasional patient with anatomical wounds of the nervous system.

Anesthetic agents depress or block the response of the autonomic nervous system. Since this response appeared activated in most battle casualties by the time of hospitalization, and since it often masked a blood volume deficiency, its depression by anesthesia often resulted in hypotension. Re-augmentation of the response by vasoconstrictors during anesthesia often appeared advantageous.

The usefulness of these drugs in the treatment of refractory, postoperative hypotension in the young, previously healthy battle casualty appeared quite limited. They occasionally seemed beneficial to the patient with a mild hypotension after massive transfusion. After the blood pressure became unobtainable, the drug could be titrated to any desired level, but the patient became refractory and, without exception, died. After developing a complete refractoriness to one vasoconstrictor, the patient sometimes demonstrated a transient sensitivity to another drug.

Although definitive studies have yet to be performed, these drugs seldom appear to meet any basic deficiency in the response of the young soldier to severe trauma. Their chief usefulness in this age group appears to be as an adjunct to anesthesia.

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Chapter 18

Anesthesia for Combat Casualties on the Basis of Experience in Korea

Robert D. Dripps, M. D.

The following observations are based on a 6-week tour of Mobile Army Surgical Hospitals in Korea in the fall of 1952. During this visit as Consultant in Anesthesiology there was opportunity to administer anesthesia of a variety of types to battle casualties personally and to observe the response of the wounded soldier to anesthesia given by personnel with varied ability. Data on the problems of anesthesia for combat casualties are included under "Tools for Resuscitation" since surgery represents a fundamental part of resuscitation and anesthesia is essential for surgery.

Experience gained in Korea did not provide much new data on the anesthetic management of the wounded. Rather it is my opinion that the basic problems involved were merely re-emphasized, and one had the disturbing impression that mankind must relearn hard-won lessons, from individual experience rather than build on knowledge previously gained. A few quotations from the British Medical Research Council's Special Report No. 26 entitled "Traumatic Toxemia as a Factor in Shock" (March 14, 1919) supports this belief. "The surgeon experienced another disappointment. If his measures were sufficient to put the soldier into a state that justified operation, this procedure produced a relapse.—A great deal of the bad effects were to be attributed to the anesthetic. Chloroform had long been recognized as dangerous, but it was more evident that ether and other anesthetics were far from harmless. Gas and oxygen was the least noxious and with its wider adoption postoperative shock greatly diminished."

The severely wounded soldier is inordinately susceptible to narcosis regardless of the agent or technic selected. Prior to anesthesia he presents a picture of apathy and depression suggestive of decreased central nervous system function. He appears to be partially narcotized already. In such a patient small amounts of central nervous depressant drugs evoke a response out of proportion to the size of the dose administered. "Normal" dosage regimens will cause death sufficiently frequently to drive this point home to the tyro. The prolonged postoperative sleep of many of these patients tends to support the above. The physiologic basis for this susceptibility is not completely understood. It is undoubtedly bound up with the numerous factors responsible for shock and hence has humoral, endocrine, toxic, hemodynamic and psychic aspects, to mention a few.

Experiences in World War I also emphasized the hazard of moving the combat casualty, the necessity for parenteral fluids, the problem of the optimal time after resuscitation for surgical intervention and the question of how much to do at a particular time. These are the crucial questions which World War II revived and which were again noted in Korea. Unless atomic or hydrogen bombs bring physiologic changes peculiar to them, one can expect future conflicts to pose the same problems.

From the standpoint of "choice of anesthesia" one can set down the following generalities.

Preoperative Medication

The use of morphine to relieve pain, to prepare an individual psychologically for operation and to reduce the amount of additional drugs needed for anesthesia has been traditional. Yet many investigators have recorded the untoward reactions of man to morphine. Its ability to impair the normal compensatory response to circulatory stress is well documented. The prolonged action of a single dose can be shown readily. Such side actions as nausea, vomiting, urinary retention and constriction of smooth muscle in the biliary and respiratory passages are undesirable. Because of tradition, however, it has been difficult to eliminate the injection of morphine. Yet morphine has little or no place in the management of the seriously wounded. Men in shock rarely complain of pain. They do complain bitterly of thirst but this is not an indication for morphine. They may be anxious and fearful. These are not indications for morphine. Beecher has suggested barbiturates. I wonder if any depressant drug is needed. The sympathetic attention of corpsmen, doctors and nurses does wonders. If, as anesthesia progresses and resuscitation becomes effective, large amounts of anesthetic drugs appear necessary, the intravenous injection of morphine, or meperidine (demerol) may be useful.

The educational campaign outlining the possibilities of harm of morphine must be continued, for although abuse of this drug is now less frequent, overdosage is still seen. Aidmen and medical officers must be made to understand the drug better. In the event of overdosage, n-allylnormorphine appears useful in reversing both the respiratory and circulatory depressant effects. This drug, which is administered intravenously, will return respiratory minute volume towards normal within 60 seconds. Its pressor effect is not as well substantiated at the moment but a blood pressure raising action has been described.

The belladonna drugs are still used and may be given intravenously as well as intramuscularly. Whether scopolamine is preferable to atropine cannot be stated with finality. The tendency of the former to produce mental aberrations is undesirable.

Choice of Anesthesia

The guiding principle for the administration of anesthesia to *any* patient is use of the least amount of narcotic compatible with the surgical requirements. As already stated, this is essential in the severely wounded. The susceptibility of the serious battle casualty to anesthesia enables one to provide satisfactory working conditions with 50 to 60 per cent nitrous oxide in oxygen in many patients. This concentration will not produce even minimal surgical anesthesia in normal individuals, but if satisfactory results can be obtained the shocked patient has been spared the consequences of a more potent depressant. This technic deserves continued application. I used it successfully in Korea, as did others to whom it has been suggested.

It is difficult to divorce the problem of selection of anesthetic agent from a consideration of the background of the anesthetist. Fortunately the training of physicians in the specialty of anesthesiology has increased greatly during the past decade. Specialists were available at the forward surgical hospitals in Korea and in installations behind these mobile hospitals. Some of these individuals were trained in one approach to the anesthetic management of the substandard patients. Others had had a different indoctrination. Since convincing proof that one agent or technic was superior to another in the management of the severely wounded was not available, it seemed wise to permit anesthetists to apply those methods with which they were most familiar. If the patient's susceptibility is kept foremost in one's thinking, this approach appears reasonable. Experience in Korea justified this approach.

Those men trained primarily in the administration of thiopental soon realized that very small doses of this drug sufficed. Profound depression of blood pressure and respiration may be produced by 25 to 50 mg. intravenously. When such was the case, it was my opinion that thiopental should be abandoned since nitrous oxide with adequate quantities of oxygen then proved sufficient. If more thiopental were required but the amounts still did not compare to those used in patients in good physical condition, this fact was constantly kept in mind lest overdosage occur. Supplementation of the thiopental with nitrous oxide-oxygen was almost invariable.

It has been stated that the induction of anesthesia with ether alone is the preferable approach to the seriously wounded. Yet I have produced severe hypotension in battle casualties with this drug in apparently very light planes of anesthesia. According to recent studies the safety of ether so far as the circulation is concerned lies in its ability to mobilize epinephrine and norepinephrine from adrenal medulla and sympathetic nerve endings. If this be prevented totally or in part ether is a potent circulatory depressant. Probably in certain seriously wounded patients such mobilization is reduced.

Observations by Zweifach and Chambers of the greater tolerance of dogs to blood loss during cyclopropane as compared to ether is corroborated by Crooke's statement during World War II that "the best anesthetic used in our shocked patients was cyclopropane," and the data of Hershey and Rovenstine on the value of cyclopropane in the management of patients with recent severe hemorrhage. I believe that this drug has a place in the anesthetic management of the battle casualty and that it does not deserve the neglect of military planners.

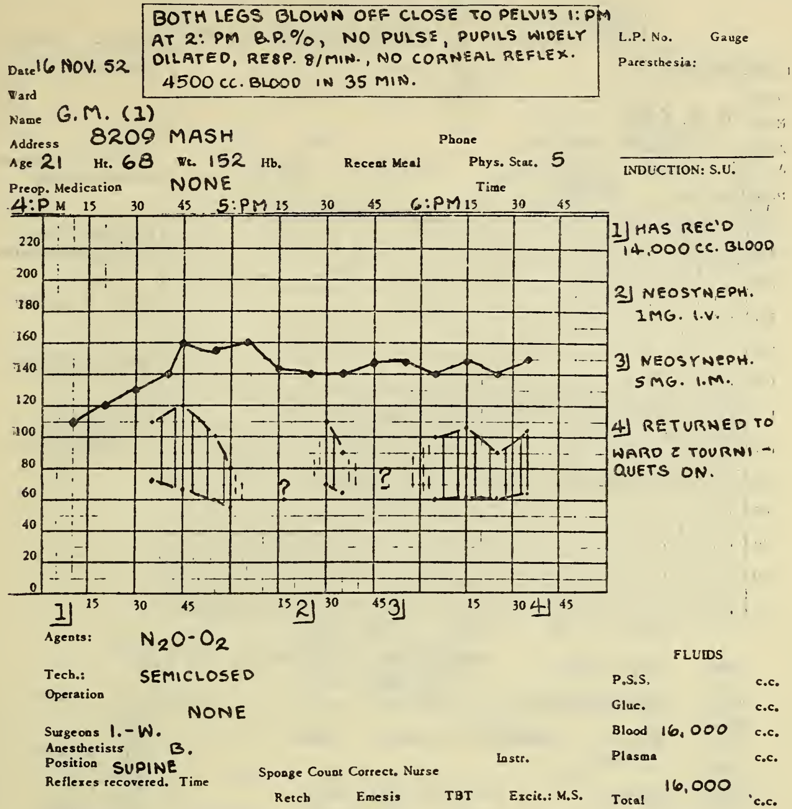
Unless it can be shown that some such technic as the use of a continuous drip of norepinephrine will maintain adequate circulation during spinal anesthesia, this method of pain relief probably has no place in the management of the seriously wounded. The circulatory alterations produced by spinal anesthesia would seem contraindicated for such patients.

For intra-abdominal operations in substandard patients, bilateral intercostal block can provide excellent muscular relaxation in light planes of general anesthesia. The block can be performed after the patient is put to sleep so that the multiple needle sticks are not objectionable. Other forms of regional anesthesia also have a place if dilute solutions are used and overdosage with its threat of hypotension is avoided. An 0.5 per cent solution of procaine is adequate for infiltration anesthesia. For nerve block, a 1 per cent solution should suffice.

The "curare" group of drugs proved of great value in Korea. d-Tubocurarine and succinylcholine were most frequently used. These substances permitted rapid intubation of the trachea and provided muscular relaxation for varying periods of time as needed. Patients in shock tended to react to succinylcholine with an exaggerated degree of muscular fasciculation. Occasionally this motor activity resembled clonic convulsions. It is possible that this represented a diminished amount of plasma cholinesterase. This deserves study as one of the derangements associated with shock.

Illustrations of some of the principles discussed above are presented in Figures 1 to 10, which are copies of anesthesia records made in Korea.

Although the surgeon assumes the major responsibility, a competent anesthetist should always be part of the team charged with resuscita-



BOTH LEGS BLOWN OFF CLOSE TO PELVIS 1:PM
AT 2: PM B.P. 0/0, NO PULSE, PUPILS WIDELY DILATED, RESP. 8/MIN., NO CORNEAL REFLEX.
4500 CC. BLOOD IN 35 MIN.

Date 16 NOV. 52
Ward
Name G.M. (1)
Address 8209 MASH
Phone
Age 21 Ht. 68 Wt. 152 Hb. Recent Meal Phys. Stat. 5
Preop. Medication NONE
Time
L.P. No. Gauge
Paresthesia:
INDUCTION: S.U.

1] HAS REC'D 14,000 CC. BLOOD
2] NEOSYNEPH. 1MG. I.V.
3] NEOSYNEPH. 5MG. I.M.
4] RETURNED TO WARD c̄ TOURNIQUETS ON.

Agents: N_2O-O_2
Tech.: SEMICLOSED
Operation NONE
Surgeons I.-W.
Anesthetists B.
Position SUPINE
Reflexes recovered. Time
Sponge Count Correct. Nurse
Instr.
Retch Emesis TBT Excit.: M.S.

FLUIDS

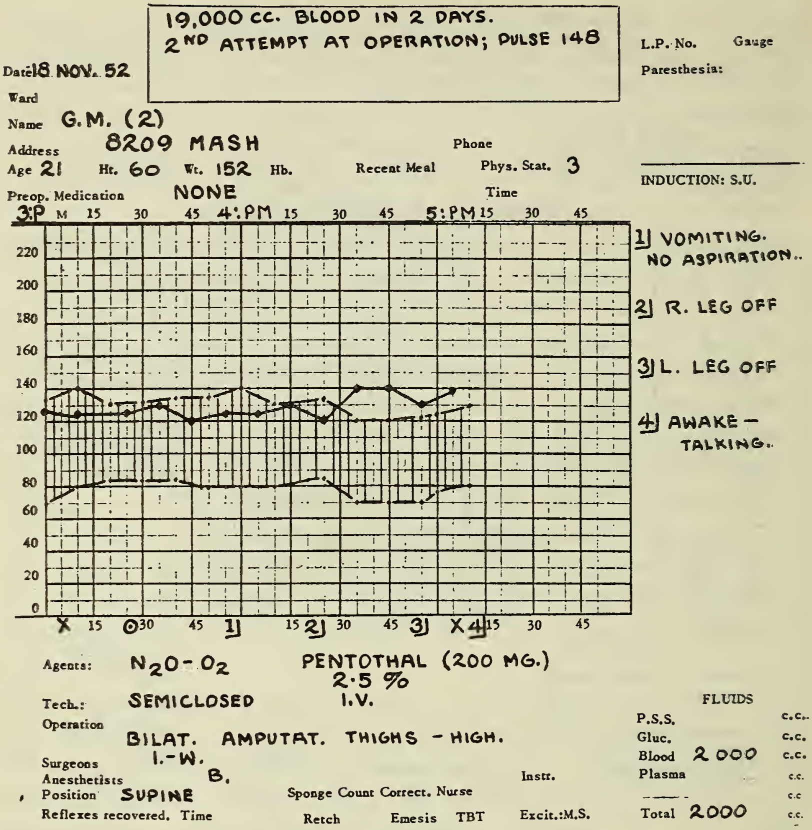
P.S.S.		c.c.
Gluc.		c.c.
Blood	16,000	c.c.
Plasma		c.c.
Total	16,000	c.c.

FIGURE 1. A 21-year-old American soldier with both legs blown off by a mine. On the left side the loss was close to the pelvis; on the right the loss occurred at the junction of the upper and middle third of the femur. Despite heroic transfusion therapy consisting of 14,000 ml. of whole blood in a period of 2 hours and with a pre-anesthetic blood pressure of 110/70 and a pulse rate of 111, attempts at anesthesia with nitrous oxide-oxygen (60 : 40) and attempts to prepare the wounds for débridement were followed by complete collapse of the circulation. Operation was therefore canceled.

tion of the wounded. From the standpoint of anesthesia the following aspects of resuscitation deserve continued study and evaluation.

1. Use of sympathetic ganglionic blocking agents or vasodilator drugs prior to the development of shock or during its treatment has been advocated by some. One of the theories behind such a suggestion is that the blood vessels can constrict *excessively* as part of compensation for hypotension. This concept was not tested in Korea.

2. The role of pressure drugs in the treatment of shock is still debated. It must be remembered that almost all of the pressure drugs except pitressin have the ability not only to constrict blood



19,000 CC. BLOOD IN 2 DAYS.
2ND ATTEMPT AT OPERATION; PULSE 148

L.P. No. Gauge
Paresthesia:

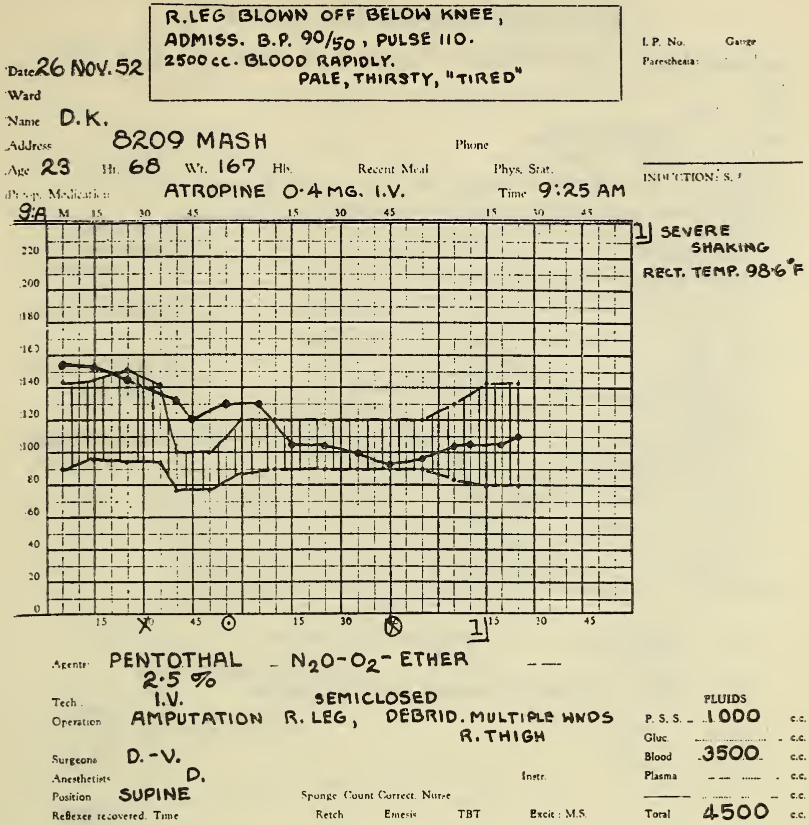
Date 18 NOV. 52
Ward
Name G. M. (2)
Address 8209 MASH
Phone
Age 21 Ht. 60 Wt. 152 Hb. Recent Meal Phys. Stat. 3
INDUCTION: S.U.
Preop. Medication NONE
Time

1) VOMITING. NO ASPIRATION.
2) R. LEG OFF
3) L. LEG OFF
4) AWAKE — TALKING.

Agents: N₂O-O₂ PENTOTHAL (200 MG.) 2.5 %
Tech.: SEMICLOSED I.V.
Operation BILAT. AMPUTAT. THIGHS — HIGH.
Surgeons I.-W.
Anesthetists B.
Instr.
Position SUPINE
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch Emesis TBT Excit.:M.S.

FLUIDS
P.S.S. c.c.
Gluc. c.c.
Blood 2 000 c.c.
Plasma c.c.
c.c
Total 2000 c.c.

FIGURE 2. The soldier discussed in Figure 1 was re-anesthetized 48 hours after the first attempt. By this time he had received a total of 19,000 ml. of whole blood, had a blood pressure of 124/70 and a pulse rate of 126. High bilateral amputation of both thighs was successfully completed under extremely light anesthesia with small amounts of thiopental and nitrous oxide-oxygen.



R. LEG BLOWN OFF BELOW KNEE,
ADMISS. B.P. 90/50, PULSE 110.
2500 cc. BLOOD RAPIDLY.
PALE, THIRSTY, "TIRED"

Date 26 NOV. 52
Ward
Name D. K.
Address 8209 MASH
Phone
Age 23
Ht. 68
Wt. 167
Hb.
Recent Meal
Phys. Stat.
Preop. Medication: ATROPINE 0·4 MG. I.V.
Time 9:25 AM

I. P. No.
Gauge
Paresthesia:

INDUCTION: S.

1) SEVERE SHAKING
RECT. TEMP. 98·6°F

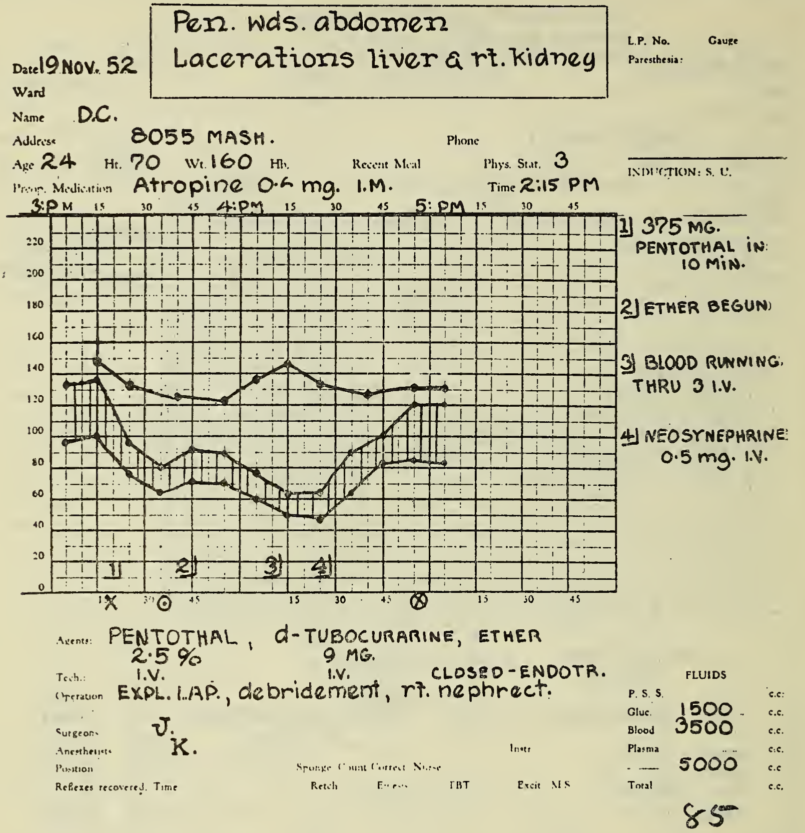
9:A
M
15
30
45
15
30
45
15
30
45
220
200
180
160
140
120
100
80
60
40
20
0
15
X
45
⊙
15
30
⊗
1)
15
30
45

Agents: PENTOTHAL 2·5 % – N_2O-O_2- ETHER ——
Tech. I.V. SEMICLOSED
Operation AMPUTATION R. LEG, DEBRID. MULTIPLE WNDS R. THIGH
Surgeons D.-V.
Anesthetists D.
Instr.
Position SUPINE
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch
Emesis
TBT
Excit: M.S.

FLUIDS

P. S. S.	1000	c.c.
Gluc.		c.c.
Blood	3500	c.c.
Plasma		c.c.
		c.c.
Total	4500	c.c.

FIGURE 3. A 23-year-old white male who was pale, "tired" and thirsty despite 2,500 ml. of whole blood. His right leg had been blown off below the knee by a mine. Blood pressure was 144/90 and pulse rate 154. The relatively high blood pressure suggested maximal efforts at compensatory vasoconstriction, and warned of hypotension with induction of anesthesia. This occurred as thiopental (200 mg.) was administered slowly over a 10-minute period. A more seriously ill casualty might have had an even greater decrease in blood pressure. Note the reduction in pulse pressure following anesthesia with thiopental.



Pen. wds. abdomen
Lacerations liver & rt. kidney

Date 19 NOV. 52
Ward
Name D.C.
Address 8055 MASH.
Phone
Age 24 Ht. 70 Wt. 160 Hb. Recent Meal Phys. Stat. 3
Preop. Medication Atropine 0.6 mg. I.M. Time 2:15 PM

L.P. No. Gauge
Paresthesia:

INDUCTION: S. U.

1] 375 MG. PENTOTHAL IN 10 MIN.

2] ETHER BEGUN

3] BLOOD RUNNING THRU 3 I.V.

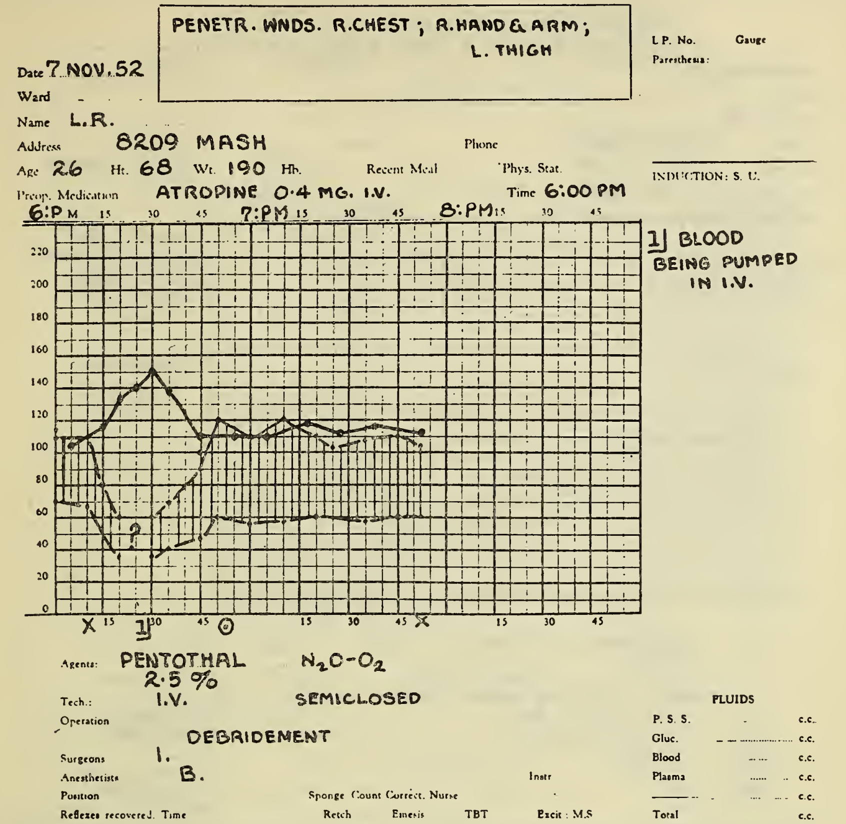
4] NEOSYNEPHRINE 0.5 mg. I.V.

Agents: PENTOTHAL, 2.5 % d-TUBOCURARINE, 9 MG. ETHER
Tech.: I.V. I.V. CLOSED-ENDOTR.
Operation EXPL. LAP., debridement, rt. nephrect.
Surgeons J.
Anesthetists K.
Instr
Position
Sponge Count Correct Nurse
Reflexes recovered. Time
Retch Emesis TBT Excit MS

FLUIDS		
P. S. S.		c.c.
Gluc.	1500	c.c.
Blood	3500	c.c.
Plasma		c.c.
- —	5000	c.c
Total		c.c.

85

FIGURE 4. A 24-year-old white male with multiple penetrating wounds of the abdomen. The pre-anesthetic pulse rate of 148 and the high diastolic pressure should have warned of circulatory instability. Induction of anesthesia with thiopental was followed by a sharp decrease in blood pressure and a narrowing of the pulse pressure. The addition of ethyl ether vapor at 4:00 p. m. brought a further reduction in arterial pressure. Five thousand ml. of fluid was administered during the operation. A pressor drug—neosynephrine—appeared of value.



PENETR. WNDS. R.CHEST; R.HAND & ARM; L. THIGH

Date 7 NOV. 52
Ward
Name L.R.
Address 8209 MASH
Phone
Age 26 Ht. 68 Wt. 190 Hb.
Recent Meal
Phys. Stat.
Preop. Medication ATROPINE 0·4 MG. I.V.
Time 6:00 PM

L.P. No. Gauge
Paresthesia:

INDUCTION: S. U.

1J BLOOD BEING PUMPED IN I.V.

Agents: PENTOTHAL 2·5 % N_2O-O_2
Tech.: I.V. SEMICLOSED
Operation DEBRIDEMENT
Surgeons I.
Anesthetists B.
Instr
Position
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch Emesis TBT Excit: M.S

FLUIDS

P. S. S.	-	c.c.
Gluc.		c.c.
Blood		c.c.
Plasma		c.c.
		c.c.
Total		c.c.

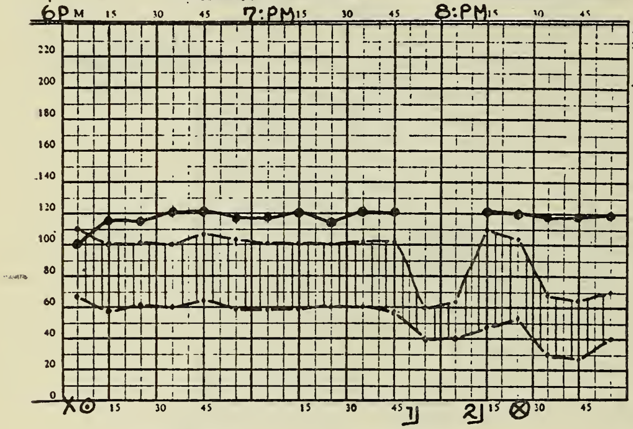
FIGURE 5. A 26-year-old white male with penetrating wounds of the right side of chest, right hand, and arm and left thigh. This soldier did not appear to be seriously wounded. The hypotension which followed the onset of anesthesia was related to a gross overdosage of thiopental. A technician anesthetist administered 1.5 gm. of this drug in 15 minutes in an effort to facilitate tracheal intubation. One cannot blame the drug in this instance so much as the way in which it was administered. It was fortunate that a fatality was averted. Had such a patient died, autopsy would have disclosed nothing and the casual recorder might have misunderstood the cause of death.

MULTIPLE WNDS. THIGHS, LEGS
Cpd. COMMIN. FRACT L. ANKLE; R. TIBIA & FIBULA; R. ULNA

I.P. No. Gauge
Paresthesia

Date 19 NOV. 52
Ward
Name D.B.
Address 8055 MASH Phone
Age 24 Ht. 66 Wt 144 Hb Recent Meal Phys Stat 3
Prep Medication ATROPINE 0·4 MG· Time 5:40 PM

INDUCTION:



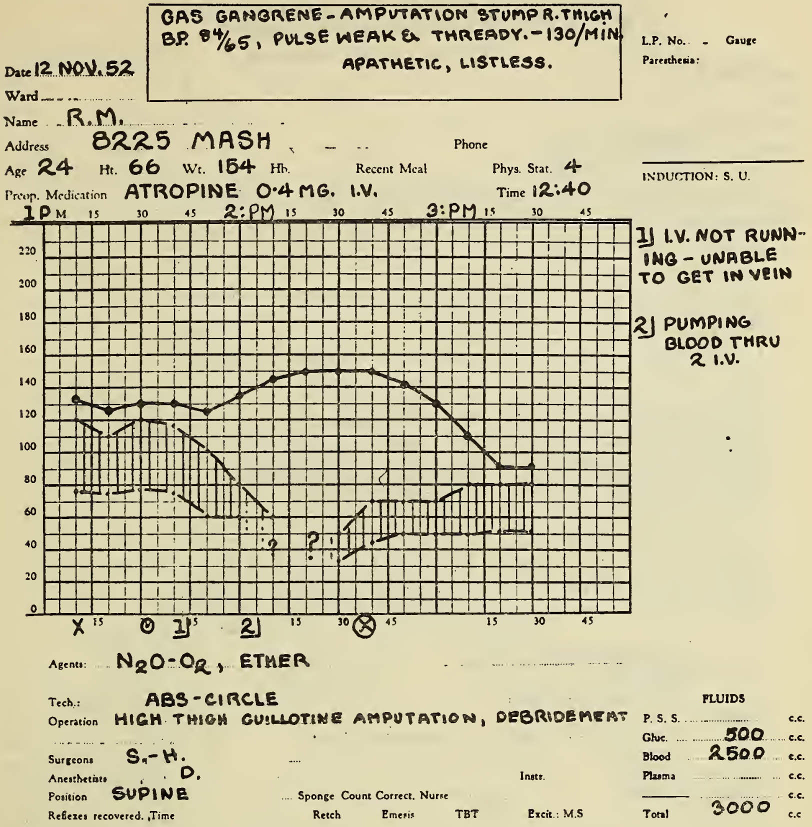
1) HICCUPS - Rx 125MG. PENTOTHAL
→ RESPIRATORY DEPRESSION +++
BP↓

2) NEOSYNEPH.
0·5 MG. } I.V.
1·0 MG.

Agents: PENTOTHAL 2·5% , N₂O-O₂
Tech.: I.V. SEMI-CLOSED
Operation DEBRID. MULTIPLE WNDS. - THIGHS, LEGS
DISARTICUL. L. FOOT
Surgeons K.
Anesthetists B. Instr
Position SUPINE Sponge Count Correct. Nurse
Reflexes recovered. Time Retch Emesis TBT Excit.: M.S

FLUIDS		
P. S. S.		c.c.
Gluc.	1000	c.c.
Blood	3000	c.c.
Plasma	—	c.c.
		c.c.
Total	4000	c.c.

FIGURE 6. A 24-year-old white male who was not in shock prior to anesthesia. After 2 hours of a satisfactory thiopental-nitrous oxide-oxygen anesthesia this patient began to hiccup. The anesthetist failed to realize that thiopental accumulates in the body as anesthesia progresses. Its rate of destruction (about 15 per cent per hour) is slower than many recognize. Injection of 125 mg. of thiopental, a dose which was well tolerated at 6:00 p. m., caused profound respiratory and circulatory depression at 7:50 p. m. Again death could have resulted had a larger dose been injected.



GAS GANGRENE - AMPUTATION STUMP R. THIGH
B.P. 84/65, PULSE WEAK & THREADY. - 130/MIN
APATHETIC, LISTLESS.

L.P. No. - Gauge
Paresthesia:

Date 12 NOV. 52
Ward
Name R.M.
Address 8225 MASH
Phone
Age 24 Ht. 66 Wt. 154 Hb. Recent Meal Phys. Stat. 4
INDUCTION: S. U.
Preop. Medication ATROPINE 0·4 MG. I.V. Time 12:40

1) I.V. NOT RUNNING - UNABLE TO GET IN VEIN

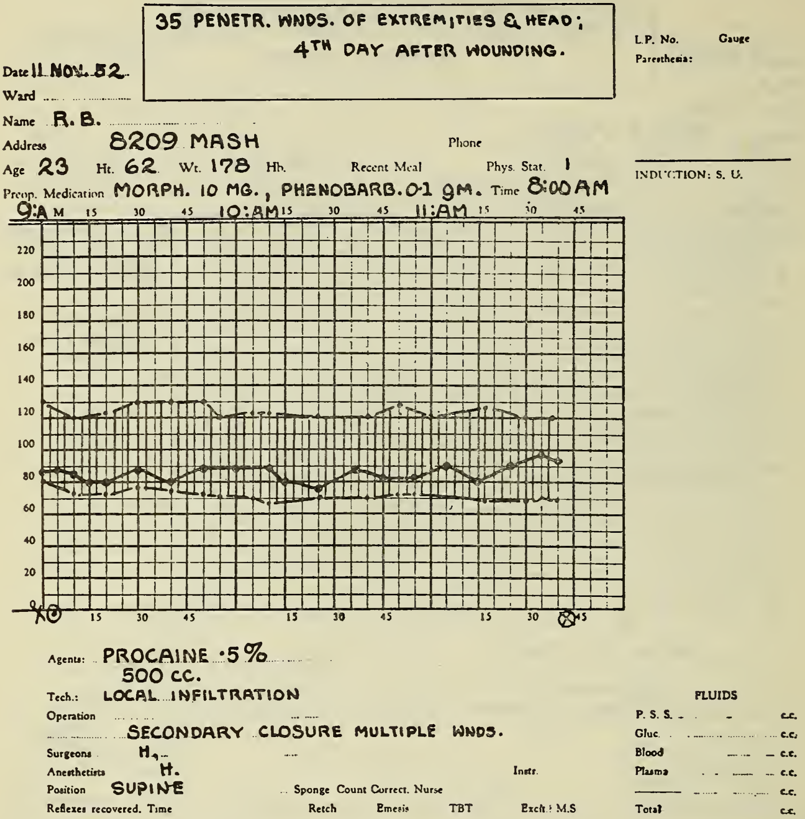
2) PUMPING BLOOD THRU 2 I.V.

1 PM 15 30 45 2:PM 15 30 45 3:PM 15 30 45
220
200
180
160
140
120
100
80
60
40
20
0
?
?
X 15 ⊙ 1) 15 2) 15 30 ⊗ 45 15 30 45

Agents: N_2O-O_2, ETHER
Tech.: ABS - CIRCLE
Operation HIGH THIGH GUILLOTINE AMPUTATION, DEBRIDEMENT
Surgeons S.-H.
Anesthetists D.
Instr.
Position SUPINE
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch Emesis TBT Excit.: M.S

	FLUIDS	
P. S. S.		c.c.
Gluc.	500	c.c.
Blood	2500	c.c.
Plasma		c.c.
		c.c.
Total	3000	c.c

FIGURE 7. A 24-year-old white male with gas gangrene in a right thigh amputation stump. Inadequate fluid therapy was partially responsible for the severe hypotension noted. Ether anesthesia, however, although only mid-first plane according to clinical signs, appeared to contribute to the profound circulatory collapse.



35 PENETR. WNDS. OF EXTREMITIES & HEAD;
4TH DAY AFTER WOUNDING.

L.P. No. Gauge
Paresthesia:

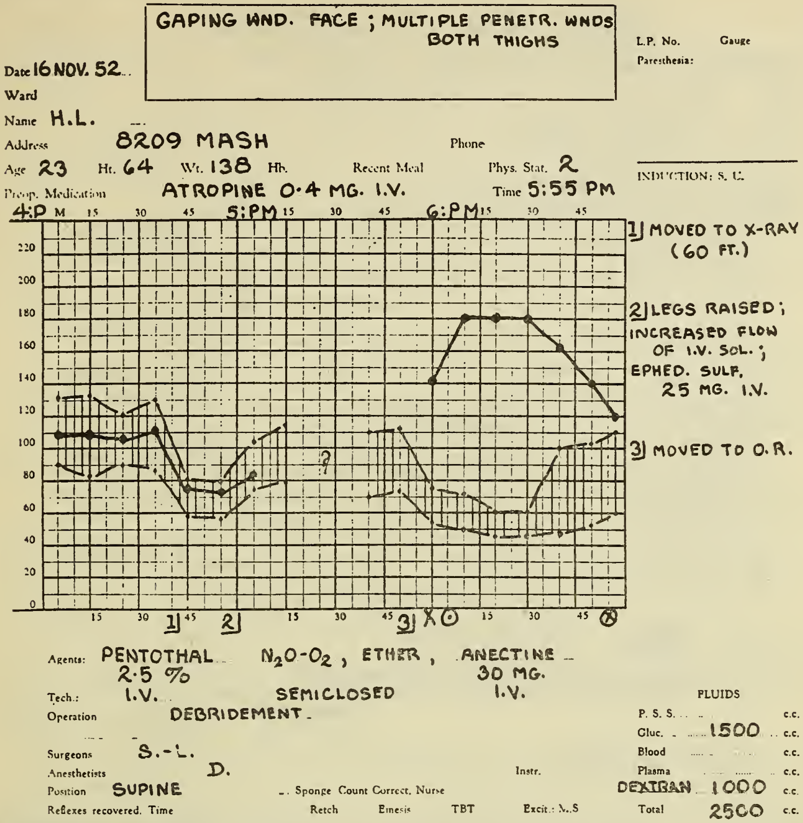
Date 11 NOV. 52
Ward
Name R. B.
Address 8209 MASH Phone
Age 23 Ht. 62 Wt. 178 Hb. Recent Meal Phys. Stat. I
INDUCTION: S. U.
Preop. Medication MORPH. 10 MG., PHENOBARB. 0.1 gM. Time 8:00 AM

Agents: PROCAINE ·5%
500 CC.
Tech.: LOCAL INFILTRATION
Operation
SECONDARY CLOSURE MULTIPLE WNDS.
Surgeons H.
Anesthetists H.
Instr.
Position SUPINE
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch
Emesis
TBT
Exch.! M.S

FLUIDS

P. S. S.	c.c.
Gluc.	c.c.
Blood	c.c.
Plasma	c.c.
	c.c.
Total	c.c.

FIGURE 8. A 23-year-old white male who did well during secondary closure of 35 penetrating wounds of the head and extremities. Operation, which required almost 3 hours, was performed under dilute procaine 0.5 per cent. The total volume of solution was high, but it must be remembered that this amount was given over a long period of time, hence toxicity of the local anesthetic proved unimportant. The value of a dilute solution of a local anesthetic in avoiding toxicity cannot be overemphasized.



GAPING WND. FACE; MULTIPLE PENETR. WNDS BOTH THIGHS

L.P. No. Gauge
Paresthesia:

Date 16 NOV. 52
Ward
Name H.L.
Address 8209 MASH
Phone
Age 23 Ht. 64 Wt. 138 Hb.
Recent Meal
Phys. Stat. 2
INDUCTION: S. C.
Prep. Medication ATROPINE 0·4 MG. I.V.
Time 5:55 PM

1) MOVED TO X-RAY (60 FT.)

2) LEGS RAISED; INCREASED FLOW OF I.V. SOL.; EPHED. SULF. 25 MG. I.V.

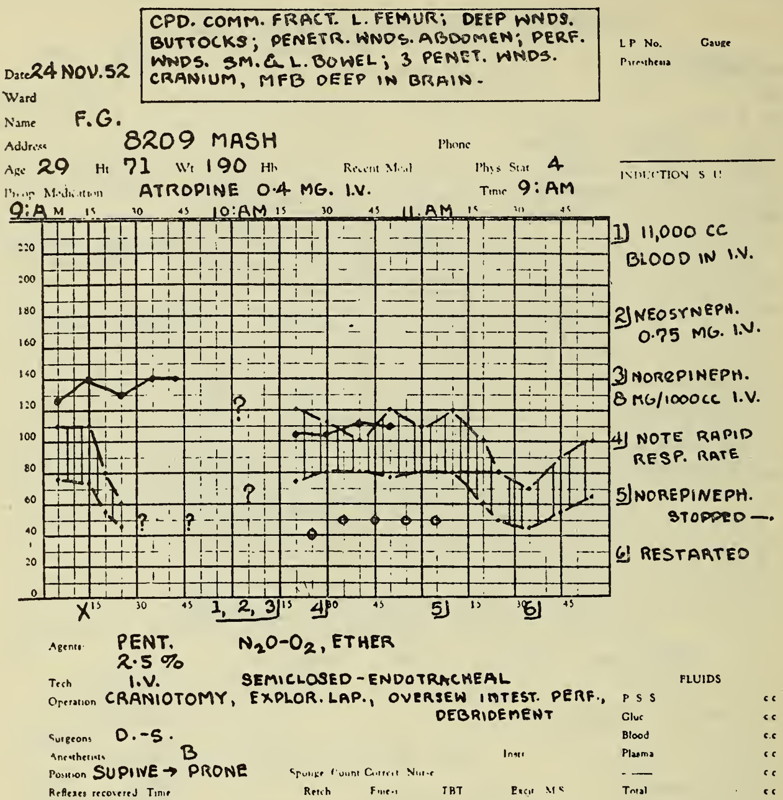
3) MOVED TO O.R.

Agents: PENTOTHAL 2·5 % N_2O-O_2, ETHER, ANECTINE 30 MG.
Tech.: I.V. SEMICLOSED I.V.
Operation DEBRIDEMENT
Surgeons S.-L.
Anesthetists D.
Instr.
Position SUPINE
Sponge Count Correct. Nurse
Reflexes recovered. Time
Retch Emesis TBT Excit.: M.S

FLUIDS

P. S. S.		c.c.
Gluc.	1500	c.c.
Blood		c.c.
Plasma		c.c.
DEXTRAN	1000	c.c.
Total	2500	c.c.

FIGURE 9. A 23-year-old white male with a large gaping wound of the face and multiple penetrating wounds of the thigh. On admission this individual was pale, thirsty, with a blood pressure of 90/70. After what appeared to be successful resuscitation with parenteral fluids, the patient was moved about 60 feet for x-ray examinations. Blood pressure promptly decreased from 130/86 to 80/60. This adverse effect of motion on the blood pressure was commonly seen. After additional efforts at resuscitation, induction of anesthesia was also followed by a decline of blood pressure from 112/72 to 60/45.



CPD. COMM. FRACT. L. FEMUR; DEEP WNDS. BUTTOCKS; PENETR. WNDS. ABDOMEN; PERF. WNDS. SM. & L. BOWEL; 3 PENET. WNDS. CRANIUM, MFB DEEP IN BRAIN.

Date 24 NOV. 52
Ward
Name F.G.
Address 8209 MASH
Phone
Age 29 Ht 71 Wt 190 Hb
Recent Meal
Phys Stat 4
Preop Medication ATROPINE 0.4 MG. I.V.
Time 9: AM

L P No. Gauge
Paresthesia

INDUCTION S U

1) 11,000 CC BLOOD IN I.V.

2) NEOSYNEPH. 0.75 MG. I.V.

3) NOREPINEPH. 8 MG/1000CC I.V.

4) NOTE RAPID RESP. RATE

5) NOREPINEPH. STOPPED —.

6) RESTARTED

Agents PENT. 2.5% N₂O-O₂, ETHER
Tech I.V. SEMICLOSED-ENDOTRACHEAL
Operation CRANIOTOMY, EXPLOR. LAP., OVERSEW INTEST. PERF., DEBRIDEMENT
Surgeons O.-S.
Anesthetists B
Inst
Position SUPINE → PRONE
Sponge Count Correct Nurse
Reflexes recovered Time
Retch Fines TBT Excit MS

FLUIDS

P S S	cc
Gluc	cc
Blood	cc
Plasma	cc
—	cc
Total	cc

FIGURE 10. A critically injured 29-year-old Negro with penetrating wounds of the abdomen, skull and lower extremities. Onset of anesthesia was followed by profound hypotension. Neosynephrine was of no value, but norepinephrine by constant intravenous infusion restored blood pressure to normal limits. Each time that the drip of this drug was slowed hypotension occurred.

vessels, but also to increase myocardial contractions. Thus, there are two problems to be evaluated: (1) Is there virtue in decreasing the vascular capacity via vasoconstriction—*venous* as well as arterial; (2) Is there utility in stimulating the heart? It was my clinical impression that pressor drugs were of value in occasional patients in Korea. Not infrequently less potent agents such as phenylephrine (neosynephrine) and methoxamine (vasoxyl) were inferior to norepinephrine (levophed), but there did seem to be a place for these substances in the management of hypotension and shock. Convincing data were not obtained, however.

3. The administration of hydrocortisone, preferably intravenously, has appeared to some civilian observers to restore vascular reactivity to pressor drugs or to the naturally occurring substances, epinephrine and norepinephrine. This concept deserves continued exploration. Korea did not add to my knowledge of this possibility.

4. The role of oxygen in the treatment of shock also remains unclear. Oxygen via nasal catheter was used in Korea as part of the resuscitation program in some casualties. Again only clinical impressions are available and these are contradictory.

5. The desirability of warming the cold battle casualty has been debated. It appeared to me that shivering, pilomotor phenomena and peripheral cyanosis from cold were unnecessary stresses for a patient but proof is lacking.

6. The adverse effect of motion on a partially resuscitated patient was demonstrated frequently. The hemodynamic alterations responsible for this remain to be demonstrated, although pooling of blood somewhere seems the best explanation.

7. The development of hypotension with the onset of general anesthesia was frequent. Presumably this represents dilation, primarily of skeletal muscle blood vessels, but this should be studied.

8. The utility of the intra-arterial route for administration of blood has been challenged convincingly in the experimental animal. Whether certain clinical impressions of the value of this resuscitation measure will ever be substantiated is uncertain at the moment. Most will agree, however, that the hazards of the method are not inconsiderable.

9. A better method for administering blood intravenously under pressure is needed. Air embolus occurred in Korea and is an unnecessary hazard of blood transfusion.

Chapter 19

The Plasma Concentration of Penicillin in Korean Battle Casualties

First Lieutenant Joseph G. Strawitz, MC, USAR
Koibong Li, M. D., Ph. D.
Lieutenant Colonel Robert B. Lindberg, MSC, USA
Major Arthur Newton, MSC, USAR
Captain John M. Howard, MC, USAR
Lieutenant Colonel Curtis P. Artz, MC, USA

This study of the concentration of penicillin in the plasma[1] was a part of a broad program of investigation of the resuscitative tools used in the emergency treatment of the wounded soldier.

At the battalion aid station, in addition to vital restorative measures, the casualty received aqueous procaine penicillin intramuscularly in a dosage of 300,000 to 600,000 units. He was then transferred via ambulance or helicopter to a forward surgical hospital arriving from 1 to 5 hours after administration of the antibiotic. Throughout this period of evacuation, casualties often remained in varying degrees of blood volume deficiency.

The purpose of this study was to determine plasma levels of penicillin in severely injured soldiers after intramuscular injection of aqueous procaine penicillin. It was believed that, in the combat casualty, the adequacy of penicillin therapy could be better assessed from these levels.

Materials and Methods

Sixty-five casualties were selected for study at the time of admission to the forward hospital. A record was kept of the amount of penicillin received, the lapse of time after injection, and the vital signs of the patient. A heparinized venous sample was obtained by aseptic technic; then the plasma was separated and placed in a sealed test tube and frozen immediately. The specimens were shipped by air to the 406th Medical General Laboratory in Tokyo. Penicillin assays were based on the inhibition of hemolytic staphlococcus (Heatly strain) by a serial dilution technic.[2] Control studies indicated that freezing did not inactivate the penicillin.

Thirty-nine patients received 300,000 units of penicillin. Of this number, 21 were considered hypotensive because the systolic blood pressure was less than 100 millimeters of mercury. Twenty-six patients received 600,000 unit of penicillin; 8 were hypotensive. Most of the casualties in the normotensive group had a blood volume deficiency, but were vasoconstricted.

Control studies of the plasma concentration of penicillin, following the intramuscular injection of 300,000 and 600,000 units of aqueous procaine penicillin respectively, were carried out in two subjects. Plasma levels were determined hourly for 6 hours post-injection.

Results

After injection of 300,000 units of penicillin, the plasma concentrations ranged up to 1.8 units per milliliter (Fig. 1). Between 1 and 6 hours after injection, only 4 casualties had a concentration below 0.2 unit per milliliter. No correlation could be made between the degree of circulatory insufficiency as determined by the blood pressure and the plasma concentration of penicillin.

Following injection of 600,000 units of penicillin, plasma levels ranged up to 2.2 units per mm. (Fig. 2). Although only six casualties had a plasma concentration below 0.2 unit per milliliter, all but three of the casualties had levels below the control values. The number of hypotensive patients was too small to permit any conclusions; however, no obvious relationship was noted between the blood pressure and penicillin concentration.

The control studies confirmed the previous observations of Romansky[1] (Figs. 1 and 2).

Discussion

Altemeier[3] and Cloud[4] and their associates demonstrated that plasma levels were higher and remained higher for a longer period in the shocked animal than in control animals, in spite of the fact that penicillin was absorbed more slowly. Although absorption was slightly delayed, higher levels resulted because urinary excretion was markedly diminished. This diminution in urinary excretion was an important factor, because 40 per cent of penicillin is normally excreted in the urine within the first hour after injection.[5]

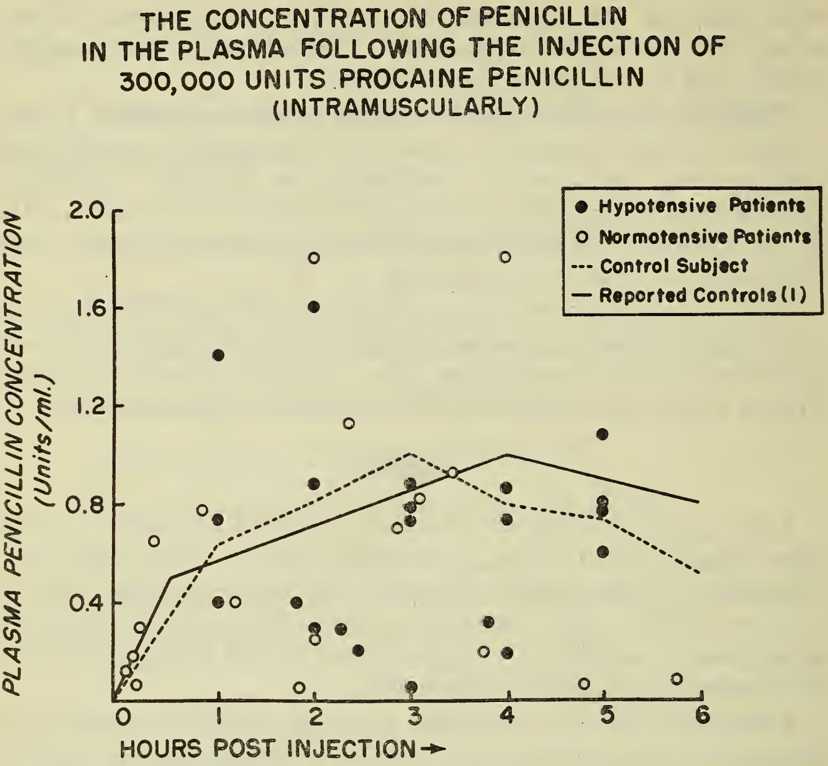


FIGURE 1. The scattergram demonstrates a wide variation in plasma concentration of penicillin following the intramuscular injection of 300,000 units of aqueous procaine penicillin. Most of the levels fall below the curves for control subjects. There appears to be no significant difference between the injured patients with normal blood pressure and those who were hypotensive.

The plasma levels obtained in this study of the battle casualty, as compared with those suggested for routine use, were well above the minimal therapeutic levels of 0.06 unit per milliliter[6] and 0.05 unit per milliliter,[7] but were often below the concentration found necessary to inhibit, in vitro, the clostridial organisms that colonized wounds of soldiers injured in Korea.[8]

Summary

Serial plasma levels were determined at varying periods up to 6 hours after the injection of aqueous procaine penicillin in 104 severely injured men. Most of the levels were below those of control subjects but well above the minimal therapeutic level. The levels obtained in hypotensive patients did not differ significantly from the levels obtained in normotensive patients.

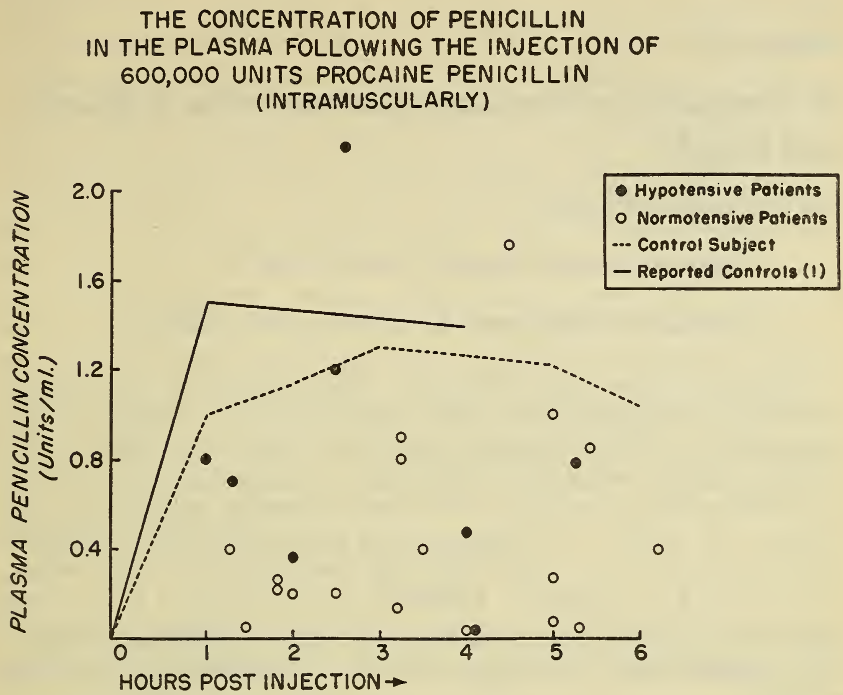


FIGURE 2. This scattergram demonstrates that the plasma concentration of penicillin following the injection of 600,000 units of aqueous procaine penicillin was usually lower than in control subjects.

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Chapter 20

A Comparison of Antibiotic Concentrations in Plasma and Muscle

An Experimental Study

Captain John D. Marshall, MSC, USAR

First Lieutenant Joseph G. Strawitz, MC, USAR

Previous studies have demonstrated the bacterial flora of combat wounds,[1,2] the sensitivities of the anaerobic flora to antibiotics,[3] and the plasma penicillin concentration in the combat casualties.[4] The purpose of the present study has been to extend these observations in the laboratory to compare the concentrations of antibiotics in the plasma and muscle. The plasma level of any particular antibiotic has been known to be higher than the concentration in most organs which have been studied.[4] Since the military surgeon is primarily interested in wound infection, this study was designed to compare the concentration in plasma with the concentration in skeletal muscles.

Materials and Methods

Rabbits, averaging 2 kilograms in weight, were selected as experimental animals. After having fasted for 24 hours, all four extremities were shaved. The appropriate antibiotic was then given intramuscularly or intravenously. The following large doses were used in order to facilitate analysis:

Procaine penicillin: 30,000 units/kg. of body weight.
Aureomycin HC1: 50 mg./kg.
Terramycin HC1: 75 mg./kg. and 250 mg./kg.
Chloramphenicol: 250 mg./kg.

Under ether anesthesia, and utilizing sterile surgical technic, blocks of skeletal muscle were taken from an extremity at hourly intervals for 4 or 5 hours. Simultaneously, heparinized blood samples were taken and the plasma was separated under sterile precautions. Care was taken not to excise muscle near the site of injection.

Maintaining sterile precautions, each block of excised muscle, weighing approximately 1 gram, was ground in the TenBrock tissue grinder. To each gram of tissue, 4 cc. of sterile saline was added, giving a dilution of 1:5. The suspension was transferred to a 15 cc.

centrifuge tube and spun at 1,500 r. p. m. for 15 minutes. The plasma and the supernatant of the tissue suspension were aseptically transferred to sterile test tubes. The plasma was diluted with saline to final concentrations of 1:10 and 1:100. Petri dishes, 15 x 150 mm., containing a thin layer of blood agar, were streaked with an 18-hour broth culture of *Shigella dysenteriae* (ES110) for chloramphenicol and terramycin sensitivities and hemolytic Staphylococcus (Heatly strain) for the penicillin and aureomycin sensitivities. Nine stainless steel cylinders, measuring 10 mm. in height, with a 10 mm. inside diameter, were placed on the surface of the plate in three rows: 0.5 ml. amounts of undiluted 1:10 and 1:100 plasma respectively were placed in the upper row cups; 0.5 ml. amounts of saline containing 100, 10 and 1 micrograms respectively of the antibiotic standard were placed in the center row as controls. In the lower row, 0.5 ml. amounts of 1:5, 1:10 and 1:100 respectively of the diluted tissue extract were placed. The Petri dishes were then incubated at 37° C for 18 hours, after which time the zones of inhibition were measured and compared using the graph method.

Four animals were studied in each series.

Results

The average hourly antibiotic levels in blood and tissue of each determination on the four rabbits studied with each antibiotic are demonstrated in Figures 1 to 5.

Penicillin

Following the intramuscular injection of penicillin, the tissue levels during the first and second hours after injection were approximately one-tenth the plasma level (Fig. 1).

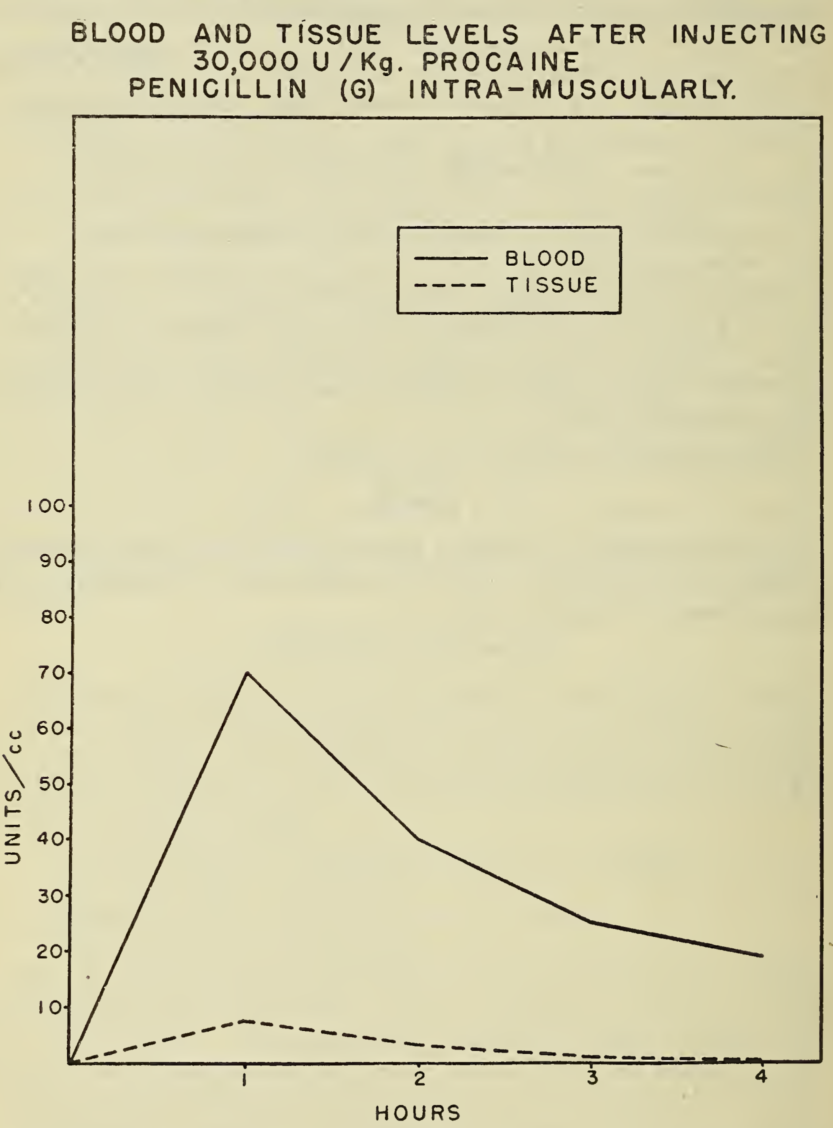

FIGURE 1. This graph, representing the average of the four rabbits studied, demonstrates the low concentration of penicillin in the muscle. This probably reflects the rapid excretion of penicillin in the urine.

Aureomycin

The intramuscular injection of aureomycin resulted in a tissue level which was approximately 70 per cent of the plasma level at 1 hour, 80 per cent of the plasma level at 2 hours, and then equaled or surpassed the plasma concentration (Fig. 2).

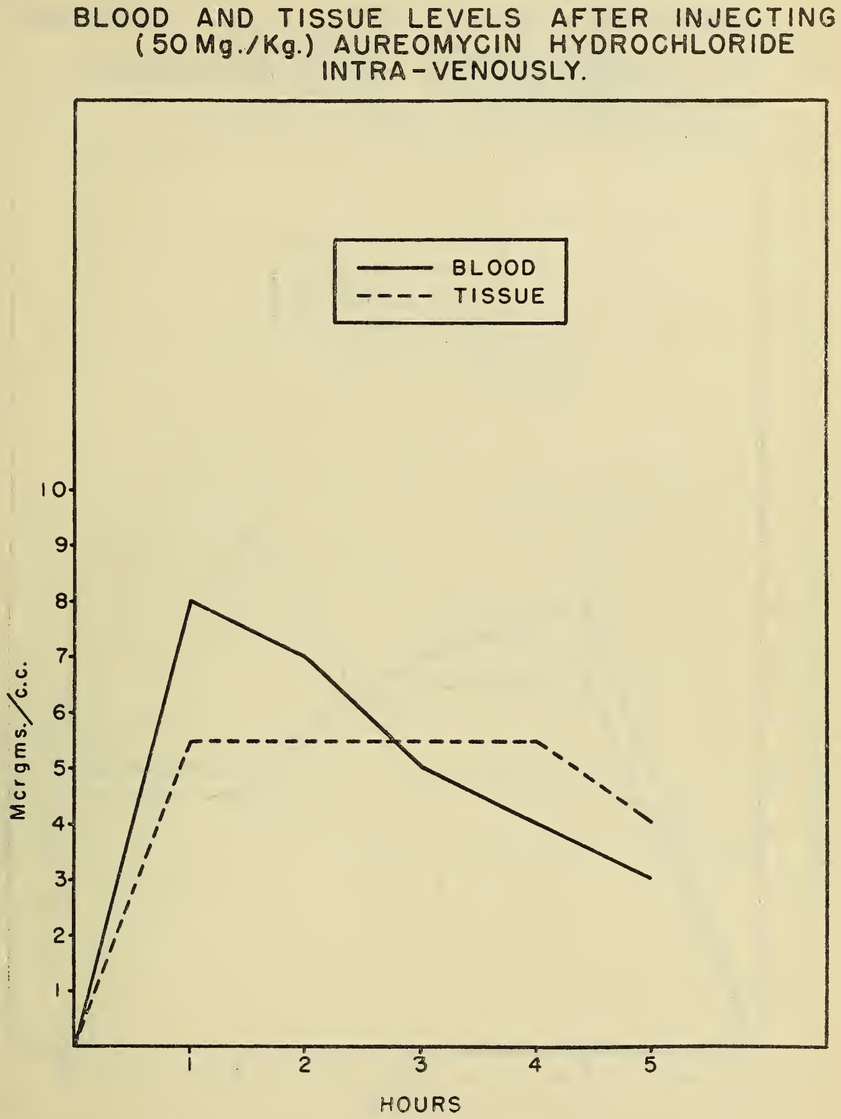
BLOOD AND TISSUE LEVELS AFTER INJECTING (50 Mg./Kg.) AUREOMYCIN HYDROCHLORIDE INTRA-VENOUSLY.

FIGURE 2. Since aureomycin is more slowly excreted, the plasma and tissue levels equilibrate at a high tissue concentration.

Terramycin

Following the intramuscular injection of terramycin (250 mg./kg.), the muscle concentration rose to 90 per cent of the plasma concentration and remained at this relative level throughout the 4-hour period of study (Fig. 3).

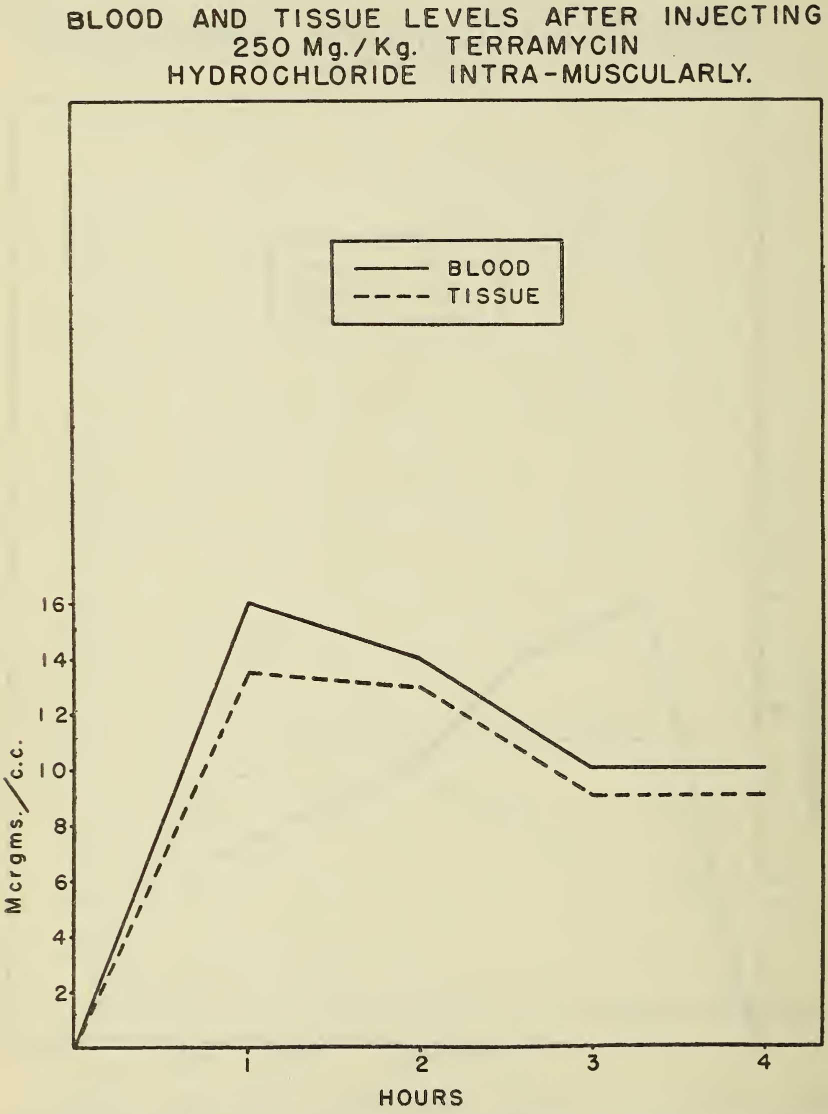

FIGURE 3. This graph, representing the average values of four experiments, demonstrates that following its injection intramuscularly the concentration of terramycin in muscle approximates the plasma concentration throughout the 4-hour period.

The intravenous injection of terramycin (75 mg./kg.) resulted in an immediate increase in the serum concentration so that at 1 hour the serum to muscle ratio was 2:1. Thereafter the serum concentration rapidly fell whereas the tissue concentration remained almost constant (Fig. 4).

BLOOD AND TISSUE LEVELS AFTER INJECTING
75 Mg./Kg. TERRAMYCIN
HYDROCHLORIDE INTRA-VENOUSLY.

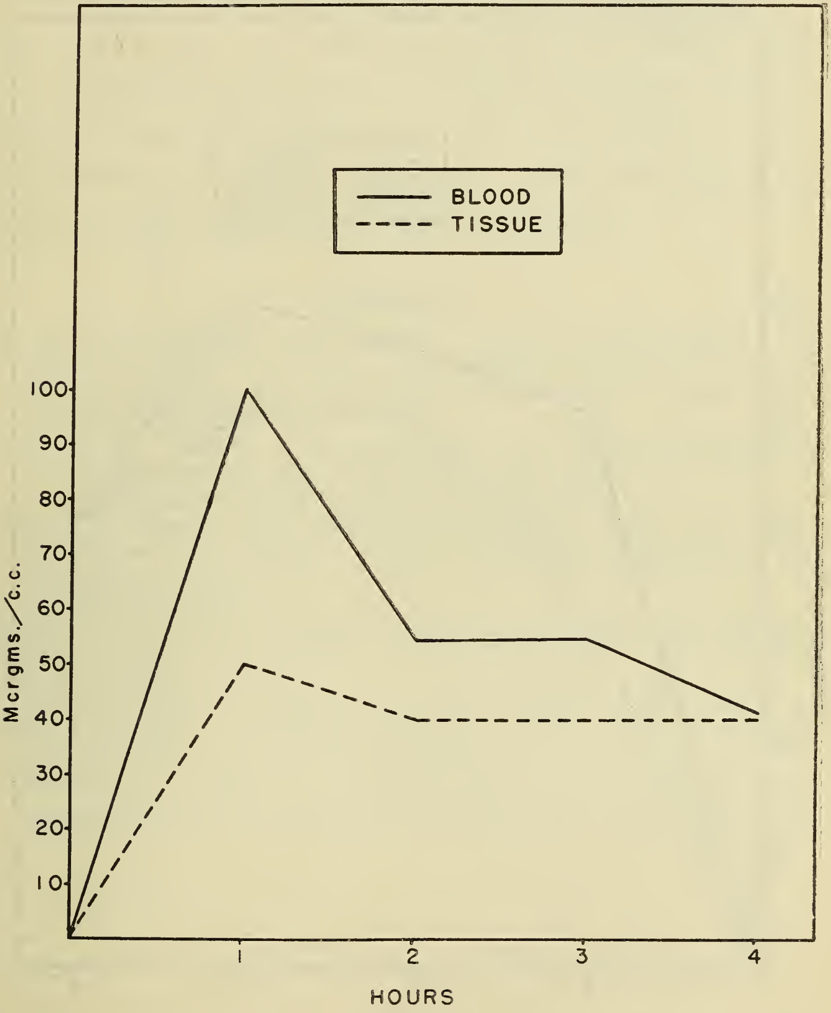

FIGURE 4. Throughout a period of 4 hours the average concentration in muscle of these four animals was over 200 per cent higher than in the preceding four who received the antibiotic intramuscularly.

Chloramphenicol

Chloramphenicol, intramuscularly, resulted in a muscle concentration of the antibiotic which ranged between 60 and 90 per cent of the plasma concentration for the first 3 hours and equaled the plasma concentration at the fourth hour (Fig. 5).

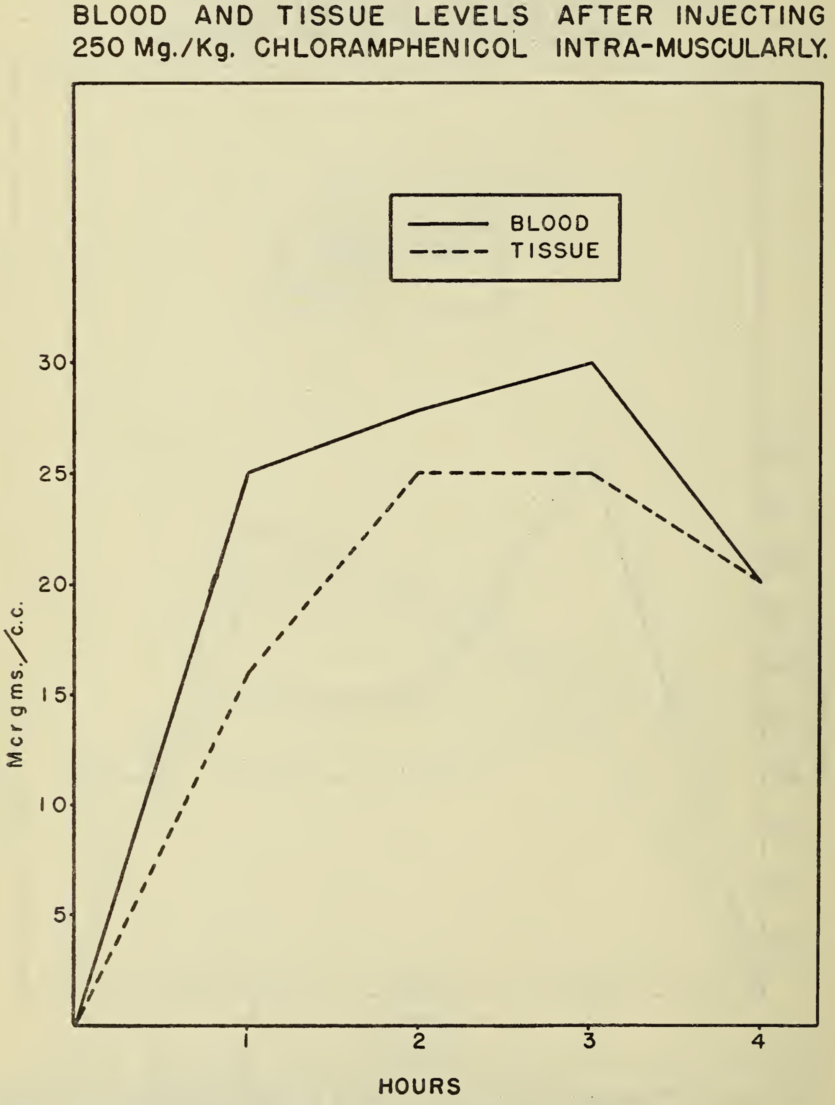

FIGURE 5. Demonstrating the close approximation of the muscle and plasma concentrations of chloramphenicol following its intramuscular injection.

Discussion

The value of a high, sustained concentration of antibiotics in the muscles has not been conclusively demonstrated but would appear a a desirable goal of therapy. Penicillin is rapidly excreted in the urine,[6] and this is probably the explanation of its low concentration in the muscle. These assays were performed on healthy muscle which had not been previously traumatized by injury or infection. It is probable that the inflammatory response to injury would result in a higher concentration of antibiotics in injured muscle.[5,7] Nevertheless, the rapid excretion and low muscle concentration of penicillin again raises a question as to whether, in the treatment of combat casualties, primary reliance should be placed on penicillin for antibiotic coverage. This question becomes even more acute when the possibility of mass casualties from atomic warfare is considered. Under such conditions, débridement might have to be postponed indefinitely and the role of antibiotic therapy would assume greater importance.

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Chapter 21

Clinical Observations of the Effect of Intravenous Calcium Gluconate on Post-transfusion Hypotension*

First Lieutenant Joseph G. Strawitz, MC, USAR
Captain John M. Howard, MC, USAR
Major Curtis P. Artz, MC, USA

One of the problems occasionally encountered in the management of seriously injured casualties is post-transfusion, postoperative hypotension. The syndrome occurs within the first 24 hours after transfusion and operation, developing in the seriously injured casualty who has been resuscitated with difficulty. Characteristically the hypotension will respond to additional transfusions although, clinically, the transfusion requirements, being large, may seem out of proportion to blood loss. Less frequently the hypotension will be progressive and refractory to subsequent transfusions and only temporarily responsive to vasoconstrictors. Autopsy of such patients usually revealed an increased weight of the lung.[1] This finding suggested the probability of pulmonary edema secondary to cardiac insufficiency.

Following the treatment of hemorrhagic shock with citrated blood in approximately 10 per cent of a series of 70 dogs, post-transfusion hypotension was found to respond to the intravenous injection of calcium lactate.[2]

Meroney and Herndon,[3] while working in the Renal Insufficiency Center in Korea, demonstrated the striking improvement in cardiac function when the hyperkalemic patient was treated intravenously with calcium solutions. Between 12 and 24 hours after injury, a transient state of hyperkalemia was noted in some of the more severely injured casualties who had not developed renal insufficiency.[4]

Scott and his associates demonstrated the marked alterations in hepatic function of the battle casualty following massive injuries.[5] Citrate metabolism was not included in their hepatic studies.

The purpose of this study was the empirical evaluation of intravenous calcium gluconate in the treatment of post-transfusion hypotension. It has been based on the hypothesis that a relative insufficiency in hepatic function following severe injury may result in a slowing of the metabolism of citrate which, as an anticoagulant, is admin-

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*Previously published in *Archives of Surgery 70*: 233, 1955.

istered in large quantities during the course of massive transfusions. This might be associated with a reduction in the concentration of ionized calcium in the serum. A reduction in the ratio of ionized calcium to potassium concentration in the serum would be even more likely, since serum potassium not infrequently rose during the postoperative period. A reduction in cardiac output might result. As the concentration of ionized calcium in the serum cannot be measured chemically, a therapeutic test of calcium appears the most direct method of approach.

Four normotensive controls, eight battle casualties, and one patient with obstructive jaundice were included in this study. Except for the last patient, all were young men in the 20- to 30-year age range who had been healthy previously.

Results

Of the four control subjects, two were normal men and two had received minor injuries. Each was observed for 1 hour following an intravenous injection of 10 cc. of 10 per cent calcium gluconate. One patient noted an increased sense of warmth; but there was no detectable cardiovascular response. The blood pressure and pulse rate were not altered.

Three patients demonstrated a striking response to calcium.

Patient 1. This 21-year-old soldier suffered shell-fragment wounds which resulted in compound, comminuted fractures of the mandible and left humerus, a perforating wound of the left shoulder, and shell-fragment wounds of the left leg and right arm.

He arrived at a forward hospital in moderate shock. Resuscitation was difficult because of a persistently bleeding lingual artery. He was given 4,500 cc. of blood preoperatively and 5,000 cc. during operation. The left lingual artery was ligated and multiple wounds were débrided. Postoperatively the systolic blood pressure remained at 80 mm. Hg and the pulse rate 120 per minute despite infusion of an additional 2,500 cc. of blood.

Five hours postoperatively, 1 gram of calcium gluconate in 10 cc. of distilled water was given intravenously over a period of from 2 to 3 minutes. There was an immediate rise in blood pressure to 120/80 (Fig. 1); and pulse rate was 120 per minute. The pulse volume and heart tones were clinically improved. There was an increase in respiratory rate and excursion.

The blood pressure was maintained at normal levels as 500 cc. of dextran and 1,000 cc. of 5 per cent glucose in water were given over a period of several hours. His subsequent course was uncomplicated.

Patient 2. This Korean soldier suffered shell-fragment wounds of the head, left thigh, right knee, and right forearm.

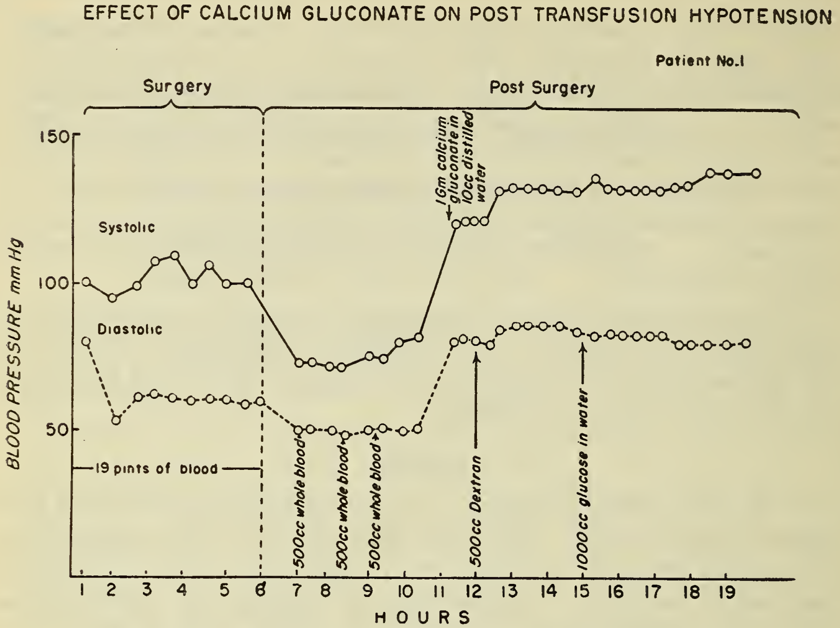

FIGURE 1. Postoperative, Post-transfusion Hypotension.

Demonstrating the striking elevation in blood pressure following the injection of calcium gluconate. This casualty had received 12,000 cc. of citrated blood.

At operation, a bony defect in the right frontoparietal region was explored and wounds of the arms and legs were débrided. The patient received 2,000 cc. of whole blood preoperatively and 2,000 cc. in the operating room.

Postoperatively, his blood pressure remained at levels between 80 and 90 mm. systolic for 3 hours. Further transfusion could not be justified on the basis of a minimal blood loss. One gram of calcium gluconate in 10 cc. of distilled water was given intravenously. Blood pressure immediately rose to 104/70 and was maintained at this level without further transfusion. Clinical improvement of the pulse volume was noted. There was an increase in respiratory rate and excursion.

This patient's subsequent course suggested that his normal pressure was approximately 105 mm. systolic, a pressure often noted among the Korean soldiers.

Patient 3. This 23-year-old American soldier was wounded by mortar-shell fragments sustaining penetrating wounds of the right arm, right lower thorax, right thigh, lower and mid-back. He was admitted to the surgical hospital in severe shock and required 3,500 cc. of blood and 1,000 cc. of dextran for immediate resuscitation.

Surgery revealed a lacerating wound of the right lower lobe of the lung, a large laceration of the right lobe of the liver, and penetrating wounds of the stomach and proximal ileum. Bleeding was controled, and repair of the bowel was performed. Because of the patient's critical condition, the soft tissue wounds of the extremities were not débrided. He was returned to the ward after having received a total of 7,000 cc. of blood and 1,000 cc. of dextran. His blood pressure and pulse were unobtainable at this time. An additional 2,000 cc. of blood was given; but no clinical improvement was observed.

Two grams of calcium gluconate were then given intravenously over a period of from 3 to 4 minutes. From an imperceptible level to 85 mm. systolic, an immediate rise in blood pressure occurred. The radial pulse became palpable and the heart tones were louder. Another gram of calcium gluconate produced an elevation to 100/50. This was maintained for 1½ hours, whereupon a sudden drop in pressure and an increase in pulse rate occurred. He was given alternate blood and dextran infusions and blood pressure and pulse were maintained for 16 hours until the patient died.

Autopsy revealed a retroperitoneal hematoma, large intraperitoneal blood clots, severe laceration of the right lobe of the liver, surgical absence of the right kidney, and marked pulmonary edema. Death may have been due to overtransfusion.

Patient 4. This patient was admitted in moderate shock with penetrating wounds of the left arm, face, and right thigh. He had a skull fracture, and a shell fragment was imbedded in the left parietal region. He also had fractures of the right humerous and left radius. A craniectomy was performed; and skull fragments were elevated and macerated brain tissue was removed. Débridement was performed on wounds of the arm and thigh. The anesthetic course was characterized by moderate hypotension. The patient had received 6,500 cc. of blood by the end of surgery. Despite continued transfusion for 3 hours following the operation, blood pressure remained between 90 and 100 systolic and pulse rate 140 per minute. He was given 10 cc. of a 10 per cent solution of calcium gluconate (1.0 gram) intravenously, causing an immediate rise in blood pressure to 120/80. The pulse rate, however, remained rapid. Subsequently there was a drop in blood pressure to 114/80 which was elevated by an additional infusion of 0.4 gram of calcium gluconate. Thereafter blood pressure was maintained at normal levels.

Patient 5. This 22-year-old Korean soldier was admitted to the surgical hospital in a moribund state, both lower limbs having been traumatically amputated through the upper thighs. In addition, there were large avulsive wounds of the arms. His blood pressure and pulse were unobtainable. Tourniquets were applied to the legs and an intra-arterial transfusion was started. After infusing a total of 10,500 cc. of blood, both intra-arterially and intravenously, the systolic blood pressure remained below a level of 80 mm./Hg. He was given 10 cc. of a 10 per cent solution of calcium gluconate intravenously over a period of 10 minutes, and his blood pressure rose to 100/70. Pulse and heart tones seemed qualitatively improved. Again, there was evidence of respiratory stimulation. This blood pressure level was maintained for 1 hour after which it dropped to the previous level. Subsequent intravenous injections of calcium gluconate produced transient rises in the blood pressure, but it was not of therapeutic value. The patient died during an extensive operative débridement.

Patient 6. This 41-year-old Korean suffered shell-fragment wounds of the lower right side of the chest and abdomen. On admission to the hospital, neither blood pressure nor peripheral pulse was obtainable.

He was given 1,500 cc. of blood intra-arterially and 2,000 cc. intravenously. After several hours of resuscitation, a thoracotomy was performed, and a rather large shell fragment was removed from the right lung. Laparotomy was then performed and multiple perforations of the duodenum were repaired. Postoperatively, his systolic blood pressure was maintained at 110 mm. for 10 hours, after which it gradually began to drop. Multiple and massive transfusions were given. Thirty hours following completion of the operation and infusion of 14,000 cc. of blood, the patient was given 1.5 grams of calcium gluconate in 15 cc. of distilled water intravenously over a period of 5 minutes. Immediately there was a rise in blood pressure from 80 to 104 systolic; and this pressure was maintained for 1 hour. Subsequently the patient was evacuated to the Renal Insufficiency Center.

Patient 7. This 23-year-old American soldier sustained a penetrating shell-fragment wound of the mid-abdomen. He was admitted to the forward hospital in deep shock; and both blood pressure and pulse were unobtainable.

He was given 4,500 cc. of blood, but remained hypotensive and had a systolic pressure below 90 mm. He was given 1.5 grams of calcium gluconate intravenously over a period of 5 minutes. There was an immediate rise in blood pressure to 118/70, with a marked improvement in pulse volume and heart tones. This blood pressure was maintained for an hour with 500 cc. of blood.

Laparotomy revealed a puncture wound of the right common iliac artery which was bleeding profusely. Upon evacuation of a large retroperitoneal hematoma, the patient's course deteriorated rapidly. He died a few minutes later.

Patient 8. This Korean soldier had a perforation of the colon and mesentery; and 2,000 cc. of blood was infused prior to operation. By the end of surgery, a total of 6,000 cc. of blood had been given to compensate for bleeding from the extensively damaged mesentery; and at this time, systolic blood pressure was 70 mm.

Despite the injection of 1.5 grams of calcium gluconate, he remained hypotensive for several hours. After infusion of an additional 1,500 cc. of blood, his blood pressure reached normotensive levels.

This patient's course again demonstrates that adequate replacement of blood volume is a prerequsite to other therapeutic measures.

Patient 9. This 60-year-old patient had obstructive jaundice, secondary to a carcinoma of the head of the pancreas.

Pancreatectomy was associated with moderate blood loss which did not appear to approach the 4,000 cc. of blood which was infused. Nevertheless, his systolic blood pressure remained from 80 to 85 mm./Hg for the last 45 minutes of the operation. Following a rapid intravenous injection of 2.0 grams of calcium gluconate, his systolic pressure rose immediately to 115 mm. This was the level at which it was subsequently maintained (Fig. 2).

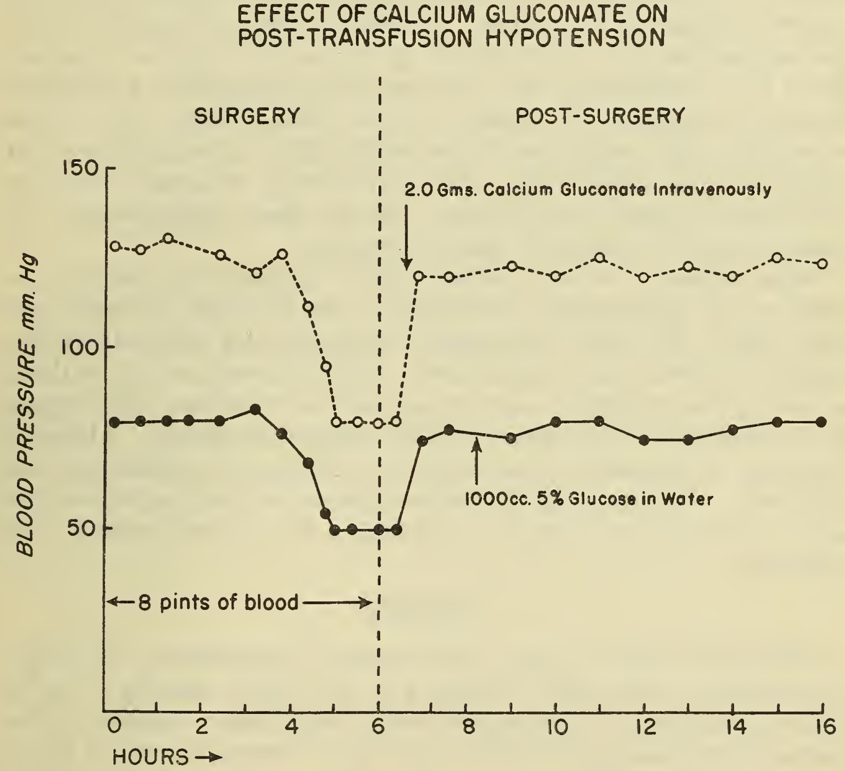

FIGURE 2. Postoperative, Post-transfusion Hypotension.

Demonstrating again the response in blood pressure following the injection of calcium gluconate. This patient, with obstructive jaundice, had received only 4,000 cc. of blood but had pre-existing hepatic damage.

Discussion

Although the effect of calcium was transient in several of the patients included in this study, and several of them died as a result of their wounds, occasionally its beneficial effect was very striking. Its effect on the blood pressure was detectable within 1 or 2 minutes following injection. Patient 8 was not the only casualty who failed to respond; he was typical of a dozen such casualties who failed to respond to the injection. Patient 9 was included in this study because the pre-existing hepatic damage and the response to calcium injection were both quite marked.

Beyond the fact that several patients demonstrated a striking response and that fact justifies further study, the results cannot yet be interpreted. The dose of calcium to be injected was selected arbitrarily. One gram of calcium gluconate contains approximately 90 mg. of calcium. If all this is made available to the body as ionized calcium it is equivalent to approximately 60 per cent of the total ionized calcium in the serum. A distinct though transient rise in the ionized calcium concentration of the serum would be expected. Since the casualty may have received the equivalent of a complete exchange transfusion of citrated, calcium-bound blood, such a dose of calcium might well assist in the body's effort in returning calcium rapidly to the ionized state. The presence of an actual deficit in the ionized calcium concentration has not been demonstrated. It may be that only a relative deficit is present.

Ionic calcium is a vital cation which, together with sodium, potassium and magnesium, contributes to the function of muscle and nerve cells. The role of the cations in maintaining adequate cardiovascular function is unquestioned. Further study of the cations, as well as the phosphate and citrate content of serum, may explain the mechanism of the cardiovascular response to calcium. Although noted as a response to the injection, respiratory stimulation was transient. By increasing the return of blood to the right side of the heart, it could have been a contributing but minor factor in the response.

Summary

Following massive injury and massive transfusion, secondary hypotension occasionally developed in the battle casualty. Under these circumstances hypotension would sometimes respond to the intravenous injection of calcium gluconate. Further study is necessary, but the clinical impression gained was that injection of calcium improved cardiac function. This was indicated by an increased quality in the heart sounds, pulse volume, and blood pressure.

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Chapter 22

Dehydration Survey in the Combat Soldier

A Study in the Korean Theater

Captain John M. Howard, MC, USAR
Captain John H. Davis, MC, USAR

The long supply lines and the mobility of the front inevitably raised difficulties to furnishing the front line soldier an adequate supply of purified water. For this reason, it was deemed advisable to gather objective evidence in order to assay the problem in Korea.

This study was carried out on the Eastern Front during the period January through July 1952. During this period the main line of resistance was stable. Supply lines were good. However, the terrain was extremely mountainous and the front lines were inevitably strung out across the top of mountain chains. Water was brought nearby in trucks but had to be carried to the top of the mountains on the backs of soldiers and laborers. Carrying the water up the mountain trail was comparable to carrying it up a flight of stairs, the equivalent of a 10- to 50-story building. A water point was thus established on top of each ridge. No reserve was maintained at this point, however, so that availability of water might vary from time to time. No severe shortage was ever reported. In spot checks, men in the front lines were systematically (daily) asked two questions: first, are the men thirsty, and second, is the water supply adequate or inadequate? Their answers had little correlation with objective evidence as illustrated by several typical observations (Table 1).

Dehydration Survey in Combat Soldier

Objective evidence was therefore sought by selecting volunteers in the front line and measuring their daily urinary output and its specific gravity. The most mountainous terrain was selected for these observations. The findings are summarized in Tables 2, 3, 4, and 5. Because of the danger inherent in the study, further observations did not seem warranted until a time when the tactical conditions might change.

Analysis of the data indicates that the lowest average urine volume occurred in January (992 ml. for 21 man days). This is entirely reasonable for the temperature was below zero (Fahrenheit) at this time. In March the average 24-hour volume was 1,344 ml. for 92 man days. In May the average volume was 1,246 ml. for 137 man days. In June and July the average volume was 1,168 ml. for 15 man days.

Table 1. Water Supply and Urinary Output

Subject	Day	Question: Is the Water Supply Adequate?	Are the Men Thirsty?	24-Hour Urinary Volume (ml.)	24-Hour Urinary Specific Gravity
Master Sergeant	1	Inadequate	Yes	2,600	1.009
	2	Inadequate	Yes	2,050	1.010
	3	Inadequate	Yes	2,100	1.015
	4	Adequate	No	3,200	1.010
Second Lieutenant.	1	Inadequate	Yes	1,450	1.020
	2	Adequate	No	1,400	1.025
	3	Adequate	No	1,000	1.030
Private	1	Inadequate	Yes	1,200	1.025
	2	Adequate	No	600	1.030
	3	Inadequate	Yes	2,200	1.012
First Lieutenant	1	Inadequate	Yes	1,275	1.020
	2	Adequate	No	1,200	1.020
	3	Inadequate	Yes	1,250	1.025
	4	Adequate	No	1,200	1.020

Table 2. Urinary Volume (Milliliters Per 24 Hours)

Date	Soldier										
	1	2	3	4	5	6	7	8	9	10	Average
1952											
29 Jan.	1,850	750	450	1,150	650	1,150	1,000	650	500	1,200	935
30 Jan.	850	1,200		1,250		1,000	850	1,200	850		1,029
31 Jan.	450	1,100		1,500		1,250					1,075
Average	1,050	1,017		1,300		1,133	925	925	675		

Average urinary volume
992 cc. 21 man days

Although there were a few instances in which the urine volume was rather low, the average for all the men on any day appeared adequate so that the supply for the area appears to have been satisfactory.

The over-all average for the 265 man days was 1,252 ml. of urine per day with a specific gravity of 1.022 (Table 6).

Finally, to note the effect of time lag after wounding, the specific gravity of the urine was measured on 25 casualties during the winter (1.025) and compared with that of 25 casualties during the summer (1.026). These measurements were made at the time the casualties arrived at the Mobile Army Surgical Hospital approximately 3.5 hours after wounding. No conclusion is justified beyond the observation that no significant difference existed.

Table 3. Volume and Specific Gravity of Urine (Milliliters per 24 Hours)

Date	Soldier 1		2		3		4		5		6		7		8		9		10		Average	
	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.
1952																						
18 Mar.	1,100	1.035	1,900	1.025	1,500	1.015	1,500	1.035	1,900	1.030	1,500	1.025	1,800	1.020	1,800	1.030	1,000	1.025	1,800	1.025	1,530	1.027
19 Mar.	1,800	1.025	1,400	1.015	1,700	1.025	2,000	1.015	1,400	1.015			1,000	1.025	2,600	1.020	1,100	1.020	1,000	1.035	1,490	1.022
20 Mar.	1,000	1.025	1,200	1.015	900	1.020	1,800	1.020	1,200	1.020	1,400	1.020	1,600	1.015	1,800	1.020	1,600	1.020	800	1.020	1,330	1.020
21 Mar.	1,800	1.020	1,100	1.020	1,700	1.020	1,300	1.020	1,100	1.025	800	1.025	1,200	1.015			1,600	1.020	900	1.020	1,029	1.021
22 Mar.	1,500	1.020	900	1.020	1,600	1.025	1,200	1.020	1,100	1.025	1,000	1.020	1,300	1.020			1,200	1.020	1,100	1.020	1,210	1.021
23 Mar.																						
24 Mar.	1,600	1.020	1,400	1.015	1,500	1.030	1,800	1.020	1,400	1.015	1,600	1.015	1,300	1.020			1,500	1.035	1,800	1.025	1,545	1.021
25 Mar.	1,800	1.020	1,100	1.020	1,400	1.015	1,300	1.020	1,300	1.020	1,000	1.020	1,300	1.020			1,200	1.020	1,100	1.020	1,150	1.020
26 Mar.	1,100	1.015	1,900	1.025	1,700	1.020	1,000	1.035	900	1.020	1,000	1.015	1,300	1.020			1,100	1.020	1,200	1.015	1,245	1.022
27 Mar.	1,200	1.015	1,000	1.020	1,600	1.015	900	1.025	800	1.025	1,200	1.020	1,400	1.020			1,000	1.025	900	1.020	1,111	1.021
28 Mar.	1,800	1.020	1,400	1.020	900	1.015	1,500	1.030	1,000	1.015	1,300	1.020	1,500	1.015			800	1.015	1,400	1.020	1,155	1.020
Average	1,470	1.022	1,330	1.020	1,450	1.020	1,430	1.024	1,210	1.021	1,200	1.020	1,370	1.019	2,067	1.023	1,210	1.022	1,200	1.022	1,394	1.021

Average volume—1,344 ml. Specific gravity—1.021
Total man days—92

Table 4. Volume and Specific Gravity of Urine (Milliliters per 24 Hours)

Date	Soldier																							
	1		2		3		4		5		6		7		8		9		10		11		Average	
	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.
1952																								
11 May	1,075	1.019	910	1.026	1,450	1.020	2,600	1.009	1,000	1.027	1,000	1.035	2,500	1.014	1,400	1.020	1,100	1.030	800	1.032	1,000	1.025	1,440	1.023
12 May	1,275	1.020	1,000	1.030	800	1.035	2,025	1.010	800	1.030	775	1.030	1,350	1.020	550	1.030			800	1.030	700	1.030	1,008	1.022
14 May	900	1.030	950	1.030	1,200	1.035	1,200	1.015	1,100	1.025	900	1.035	600	1.030	1,100	1.030	850	1.035	700	1.030	425	1.040	912	1.030
15 May	1,400	1.020	1,200	1.025			2,100	1.015	1,450	1.020			1,450	1.025	725	1.030	600	1.035	1,150	1.025	400	1.035	1,284	1.025
16 May	1,250	1.025	1,300	1.022			3,200	1.010	1,300	1.025	600	1.035	1,700	1.022	950	1.017	1,000	1.030	1,100	1.030	900	1.032	1,430	1.025
17 May	700	1.025	800	1.033	1,400	1.025	2,500	1.009	1,100	1.035			1,300	1.018	600	1.030	600	1.032	500	1.025	850	1.032	1,035	1.026
18 May	1,500	1.020	1,000	1.025	1,000	1.025	2,000	1.010	800	1.035			1,300	1.022			500	1.030			625	1.032	1,090	1.024
19 May	1,500	1.017			1,000	1.030	2,800	1.010	1,700	1.020	900	1.025							1,200	1.030	1,100	1.028	1,456	1.025
20 May	1,400	1.020	1,000	1.022	1,200	1.032	2,500	1.014	1,000	1.030	1,000	1.030	1,400	1.015			800	1.025	1,250	1.028	1,100	1.025	1,265	1.024
21 May	1,200	1.020	600	1.030	1,250	1.020	3,000	1.005	1,200	1.025	1,200	1.030	1,500	1.015			600	1.025	1,250	1.025	950	1.027	1,275	1.022
22 May	1,400	1.018	600	1.028	650	1.028	3,200	1.007	1,100	1.023	850	1.027	1,250	1.009			700	1.026	1,000	1.033	1,400	1.024	1,225	1.022
23 May	1,800	1.015	2,200	1.012	1,000	1.030	3,000	1.008	2,700	1.015	1,200	1.016	1,000	1.020					600	1.030	1,100	1.022	1,700	1.017
24 May	1,100	1.024	800	1.020	1,175	1.030	3,000	1.010			1,250	1.020	1,200	1.019					1,150	1.025	800	1.020	1,309	1.021
25 May	1,200	1.020	950	1.020	1,000	1.029	3,100	1.009			1,250	1.018	1,350	1.015					1,050	1.024			1,100	1.019
26 May	1,100	1.017	1,000	1.015			3,200	1.008			1,250	1.020	1,200	1.017					1,400	1.020	1,100	1.020	1,466	1.015
Average	1,250	1.021	1,022	1.024	1,094	1.028	2,628	1.010	1,271	1.026	1,015	1.027	1,365	1.019	888	1.026	750	1.030	996	1.028	896	1.028		

Average volume—1246 ml. Specific gravity—1.023
Total man days—137

Table 5. Volume and Specific Gravity of Urine (Milliliters per 24 Hours)

Date	Soldier															
	1		2		3		4		5		6		7		8	
	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.	Vol.	Sp. Gr.
1952																R
30 Jun.	525	1. 020	3, 200	1. 020					1, 400	1. 013	1, 200	1. 015	900	1. 018	1, 445	1. 017
1 Jul.	1, 200	1. 012	800	1. 027	600	1. 030	2, 000	1. 020	1, 150	1. 012	750	1. 018			1, 083	1. 019
2 Jul.	900	1. 021	900	1. 027					1, 100	1. 023	900	1. 030			925	1. 025

Average volume—1168 ml. Specific gravity—1.020
Total man days—15

Table 6. Dehydration Survey in the Combat Soldiers

Date	Man Days	Average Urinary Volume (ml. per 24 Hours)	Average Specific Gravity
January 1952	21	993	
March 1952	92	1, 344	1. 021
May 1952	137	1, 246	1. 023
July 1952	15	1, 168	1. 020
	265 total	1,252 average	

Clinically dehydration was not noted. Thirst is an immediate result of severe injury and does not necessarily signify dehydration immediately after injury.

Summary

During the period January–July 1952, studies of the daily urinary output of soldiers on the front lines of the Eastern Front in Korea demonstrated no evidence of dehydration.

Appendix

Daily Temperature Record

(Fahrenheit)

Combat Area—Eastern Korea

1952

Temperature

Date	1200 Hours		2400 Hours		Date	1200 Hours		2400 Hours	
	Dry	Wet	Dry	Wet		Dry	Wet	Dry	Wet
April 3	58	50	40	38	May 1	84	70	56	50
4	58	49	42	40	2	78	63	56	52
5	71	55	48	46	3	77	65	62	57
6	70	50	41	41	4	66	59	53	50
7	55	50	46	44	5	71	57	51	46
8	72	59	52	47	6	75	58	61	52
9	74	68	51	48	7	72	62	60	52
10	50	47	52	49	8	70	57	54	45
11	62	52	54	49	9	74	60	58	48
12	57	50	50	49	10	73	60	57	50
13	46	42	36	36	11				
14	51	45	43	42	12	79	61	55	49
15	43	41	38	36	13	80	65	60	52
16	52	47	59	51	14	83	66	63	56
17	54	51	42	38	15	74	60	60	53
18	53	46	46	42	16	84	65	66	59
19	34	32	38	35	17	80	64	68	60
20	49	43	42	39	18	83	67	65	53
21	55	52	35	33	19	71	59	62	55
22	56	48	40	37	20	78	63	60	55
23	57	46	40	38	21	82	65	60	54
24	62	50	46	43	22	87	66	63	52
25	64	54	44	43	23	74	59	52	50
26	56	48	43	41	24	71	53	54	48
27	63	52	49	44	25	77	63	57	52
28	55	52	53	50	26	73	59	64	56
29	68	52	48	45	27	80	67	63	58
30	73	63	54	50	28	80	71	63	58
					29	81	70	59	56
					30	55	51	57	51
					31	74	64	58	53

Temperature

Date	Maximal	Minimal	Date	Maximal		Minimal	
	Dry	Dry		Dry	Wet	Dry	Wet
June 1	79	54	July 1	90	77	72	71
2	77	52	2	80	73	67	66
3	63	56	3	78	69	63	61
4	73	53	4	83	71	62	60
5	78	53	5	81	70	58	57
6	83	53	6	81	70	64	63
7	87	52	7	83	73	64	63
8	71	56	8	80	69	63	62
9	82	55	9	76	68	63	62
10	68	56	10	80	69	65	63
11	73	56	11	82	72	63	62
12	81	55	12	90	78	62	60
13	83	60	13	87	73	64	62
14	89	67	14	79	69	60	57
15	92	57	15	75	69	66	64
16	87	63	16	88	76	68	65
17	79	62	17	80	74	73	70
18	84	63	18	88	76	72	70
19	87	64	19	75	72	72	68
20	85	58	20	84	75	70	68
21	88	57	21	83	73	68	67
22	92	58	22	90	75	67	66
23	91	61	23	88	75	67	66
24	96	60	24	88	75	69	68
25	98	65	25	80	72	69	67
26	98	64	26	74	72	66	66
27	93	63	27	70	69	66	66
28	90	67	28	71	69	64	64
29	76	69	29	70	70	66	66
30	78	68	30	75	74	66	66
			31	77	74	69	68

Temperature

Date	Maximal	Minimal	Date	Maximal		Minimal	
	Dry	Dry		Dry	Wet	Dry	Wet
August 1	88	74	September 1	74	67	58	58
2	76	65	2	74	67	57	57
3	87	68	3	62	62	59	59
4	88	65	4	70	65	59	59
5	90	64	5	75	66	59	59
6	91	65	6	78	70	59	59
7	92	67	7	71	68	59	59
8	87	68	8	77	68	56	56
9	90	67	9	79	68	58	58
10	91	68	10	78	69	58	58
11	92	70	11	74	67	62	62
12	94	70	12	71	66	58	57
13	88	72	13	62	60	56	56
14	94	74	14	66		57	
15	90	70	15	71	67	54	54
16	91	70	16	68	61	52	52
17	90	69	17	68	58	48	46
18	80	69	18	69	61	43	42
19	79	69	19	71	62	53	52
20	86	64	20	65	58	49	48
21	87	69	21	69	58	46	46
22	85	53	22	65	60	44	43
23	74	66	23	76		58	
24	75	70	24	59	58	56	55
25	74	68	25	58	58	47	47
26	71	68	26	61	58	41	41
27	85	64	27	63	55	38	37
28	70	65	28	60	55	46	45
29	76	62	29	59	57	40	39
30	82	63	30	64	56	39	38
31	75	68					

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